Steady-State Analysis of Auditory Evoked Potentials over a Wide Range of Stimulus Repetition Rates: Profile in Children versus Adults

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Abreena I. Tlumak

State University of New York at New Paltz, M.S.Ed., 1998

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This dissertation was presented

by

Abreena I. Tlumak

It was defended on

November 10, 2009

and approved by

J. Robert Boston, Ph.D., Professor, Department of Electrical and Computer Engineering

Diane L. Sabo, Ph.D., Associate Professor, Department of Communication Sciences and Disorders

Sheila R. Pratt, Ph.D., Associate Professor, Department of Communication Sciences and Disorders

Dissertation Chair: John D. Durrant, Ph.D., Professor and Vice Chair of the Department of Communication Science and Disorders

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Abreena I. Tlumak, Ph.D.

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This study profiled auditory steady-state response amplitudes in children (i.e., six to nine years of age) and in adults (i.e., 18 to 35 years of age) over a wide range of repetition rates, specifically a range well embracing component waves of conventionally stimulated and recorded transient auditory evoked responses. Response amplitudes were measured at repetition rates from 0.75 to 80 Hz. Repetition rates of 10 Hz or less have received little attention in the context of the ASSR approach which is speculated to provide technical advantages, if not additional information, to the more traditional transient protocols, at least for some applications as follows: (1) to permit characterization of subject age-dependent amplitudes; (2) to allow an exploratory examination of the effects of repetition rate on response amplitude during natural sleep, to demonstrate if results differed from those obtained when subjects were awake, and (3) to explore the use of both the fundamental and harmonics in the characterization of the response amplitude versus the typical measure of amplitude in transient analysis. Planned comparisons were conducted to evaluate the amplitude differences observed between the age groups (i.e., children and adults) and between arousal conditions (i.e., adults awake and adults asleep) across modulation frequencies.

The results of this study show that the amplitude was largest at the two lowest modulation frequencies for both adults and children. Furthermore, response amplitudes for children were significantly higher than those for adults at all modulation frequencies up to 5 Hz. Response amplitudes for adults during sleep also were significantly higher than those responses

of adults while awake at 0.75 and 1.25 Hz. Good reliability overall was observed for these response measures in both adults and children. An amplitude measure defined as the harmonic sum yielded results paralleling the profile of response amplitudes as a function of repetition rate that may be extracted from the literature, although with some differences, the significance of which remains to be determined. Of pragmatic importance is that this profile could be determined without subjective wave identification and/or interpretation and thus by a method that is inherently more objective than conventional, transient AEP tests.

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PREFACE

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1.0 INTRODUCTION

Auditory evoked potentials (AEPs) reflect electrical activity within the auditory system that is elicited by acoustic stimuli. The AEP metric represents a continuum of receptor and neurogenic potentials that are generated along the entire length of the auditory pathway. The rate of maturation--or the time it takes AEPs to reach well-defined adult waveforms--is dependent upon structural and functional development--maturational effects of myelination, synaptic density and neuro-plasticity of the neural pathways specific to individual AEP components. Thus, the rate of maturation is not uniform for all AEPs. Consequently, maturation can be monitored through changes in AEP amplitude and/or latency functions over time. Studies of age-related amplitude and latency have revealed that maturation of peripheral transient, early-brainstem components (i.e., auditory brainstem response [ABR]) is relatively short, reaching maturity by approximately two years of age. Since there are few recording limitations, the maturation sequence of the ABR has been well-defined in infants and young children. In contrast, several pioneering studies have revealed that maturation of central transient, upper-brainstem-to-cortical components (middle latency response [MLR]) and late-cortical components (long latency response [LLR]) is relatively long, reaching maturity by between 12 and 17 years of age, respectively. Because of various recording limitations (e.g., subject state) and the instability of responses at different ages, the maturation sequence of the MLR and LLR have not been well characterized in infants and young children (cf. Subsection 3.4). In general, a particular challenge for researchers and

clinicians alike is potential difficulties, if not ambiguities, of wave identification over the course of maturation. The potential for confounds exist any time the latency of a wave changes more than its own period.

Examining AEPs and/or changes in AEPs over time also can reveal the status of the auditory pathway. Clinical observations have revealed that impairment of the auditory pathway (e.g., via central nervous system [CNS] disorders and trauma) differentially affects amplitudes and latencies of the AEPs. Evoked potentials have provided the bases for useful neurodiagnostic tools and, in a variety of CNS disorders, yield predictable changes in waveform morphology (cf. Subsection 3.1). In addition, numerous investigators have examined the prognostic power of early-brainstem and exogenous cortical components in patients after head injury. Results suggest that transient AEPs provide a useful prognostic tool when employed along with other neurological tests, for example by reinforcing the prediction of the return, or not, to consciousness in trauma patients (cf. Subsection 3.7).

Thus, traditional transient AEPs can provide a way by which to measure maturation of peripheral and central auditory function, as well as to obtain a global view into the integrity of the auditory pathway. As such, they have not only provided a basis for normative values by which progress or delay in maturation or impairment can be measured, but also a foundation by which optimal stimuli and recording parameters have become standardized for the clinical application of transient AEPs. In particular, age-corrected norms are essential to the separation of maturational and pathological changes in the AEPs.

However, there is a fundamental shortcoming of conventional AEP testing that potentially limits the teasing out of maturational effects and/or the establishment of age-corrected norms difficult. This short-coming derives from the way AEPs are traditionally analyzed,

basically an approach dependent largely upon subjective waveform identification (i.e., examiner judgment). Namely, the stimulus-related response is only known in general form and must be extracted from a background of noise from which it is difficult to distinguish (i.e. convincing response-like signals may be seen in the absence of stimulation or so-called control recordings). In general, the response is not predicted well by the stimulus; it is the impulse response of a system whose transfer function is not known precisely. The identification of EP waveforms thus is relatively difficult, and even more so when looking across development--especially in young children for middle and late components. Likewise, when cortical function is reduced, waveform identification of the MLR and LLR is extremely challenging--especially with the diversity of focal injuries that can occur. Thus, there is a need for a substantially different way to evaluate AEPs themselves and for the purposes of looking across normal and injured brain development. A more deterministic-like approach clearly would be more desirable, that is an approach wherein the stimulus function predicts the response function. The steady-state stimulus and analysis technique potentially offers such an approach. A particular (potential) advantage is that such an approach lends itself to statistical techniques (Anderson, 1958; Cooley & Tukey, 1965; Dobie & Wilson, 1989; Fridman et al., 1984; Goldberg & Brown, 1969; Hotelling, 1931; Mardia, 1972; Picton, Dimitrijevic, John & Van Roon, 2001; Valdes et al., 1997; Victor & Mast, 1991; Zurek, 1992) by which to objectify response measurement and perhaps simplifying interpretation.

In adults, auditory steady-state response (ASSR) amplitude is characterized as having a primary peak near 40 Hz (Artieda et al., 2004; Azzena et al., 1995; Cohen, Rickards & Clark, 1991; Galambos, Makeig, & Talmachoff, 1981; Hari, Hämäläinen, & Joutsiniemi, 1989; Kuwada et al., 2002; Kuwada, Batra, & Maher, 1986; Levi, Folsom, & Dobie, 1993; Linden, Campbell, Hamel & Picton, 1985; Picton, Skinner, Champagne, Kellett, & Maiste 1987; Rees, 1982; Rees,

Green, & Kay, 1986; Ross, Borgmann & Draganova, 2000; Stapells, Linden, Suffield, Hamel & Picton, 1984; Stapells, Galambos, Costello, & Makeig, 1988; Stapells, Makeig & Galambos, 1987; Suzuki & Kobayashi, 1984), with additional peaks at lower modulation frequencies between 10 and 20 Hz (Ross et al., 2000; Stapells et al., 1984), and at higher modulation frequencies between 80 and 110 Hz (Artieda et al., 2004; Cohen et al., 1991; Kuwada et al., 2002; Lins, Picton, Picton, Champagne, and Durieux-Smith, 1995; Rees, 1982; Ross et al., 2000). Numerous studies have examined the effect of modulation frequency on the ASSR amplitude. However, to a great extent, response amplitude only has been described well in adults at modulation frequencies down to 10 Hz (cf. Subsection 3.5.2.1). Although, a few investigators have examined response amplitudes at modulation frequencies below 10 Hz (Picton, et al., 1987; Rees, 1982; Rees et al., 1986), this area has not been investigated thoroughly.

In adults, ASSR latency (i.e., derived from phase) is associated with corresponding transient-AEP latency windows (Cohen et al., 1991; Cone-Wesson, Dowell, Tomlin, Rance, & Ming, 2002; Herdman et al., 2002; Kuwada et al., 2002; Levi et al., 1993). In other words, long latency transient potentials require very low repetition rates or correspondingly, very low modulation frequencies to elicit a response. Therefore, ASSRs elicited at very low modulation frequencies (i.e., <20 Hz) will result in a response dominated by activity from the auditory cortices--presumably in common with the generators responsible for the production the LLR. Likewise, ASSRs elicited at low modulation frequencies (i.e., between 20 and 40 Hz) will result in a response dominated by the auditory midbrain--presumably in common with generators responsible for the production of the MLR. High modulation frequencies (i.e., >60 Hz) will

result in a response dominated by the auditory brainstem--presumably in common with generators responsible for the production of the ABR.

Although several studies have examined the effect of modulation frequency on ASSR latency, the majority of investigations have only studied those modulation frequencies 60 Hz and above and in the vicinity of 40 Hz. Investigators agree that the "80-Hz" and "40-Hz" ASSR (as they have been designated, for simplicity) corresponds to the ranges of latencies characteristic of the ABR and MLR, respectively. However, to date, only two studies have examined the effect of very low modulation frequencies, lower than 10 Hz or correspondingly, the latencies characteristic of the LLR (Picton, et al., 1987; Rees et al., 1986). Thus, like ASSR amplitude, latency functions have not been completely characterized in adults.

In addition, ASSR measurements are not completely characterized in adults or children in sleep. Although several studies have examined the effects of repetition rate on response amplitude and latency during sleep, these investigations have only explored those modulation frequencies 10 Hz and above (Levi et al., 1993; Linden et al., 1985; Picton, John, Purcell, & Plourde, 2003). The effect of sleep on ASSR is unclear for very low modulation frequencies, lower than 10 Hz or correspondingly, the repetition rates characteristic of the LLR. Interest in such results derives from the necessity of keeping subjects fully alert during testing, especially young children in assessing the more rostrally generated potentials. Thus, there is a need to examine the effects of repetition rate on response amplitude during sleep in adults (first), which will then help predict the level of concern about the effects of sleep in children.

In infants and young children, the effect of modulation frequency on ASSR amplitude has been examined in several research studies; however, outcomes were equivocal at best. Some studies reported that responses were highest in amplitude when tones were modulated at 20 Hz

(Fifer, 1985; Suzuki & Kobayashi, 1984); other investigations reported that responses were highest in amplitude when tones were modulated at frequencies between 25 and 40 Hz (Pethe, Mühler, Siewert, & Specht, 2004; Riquelme, Kuwada, Filipovic, Hartung, & Leonard, 2006) or between 72 and 97 Hz (Aoyagi et al., 1994; Aoyagi et al., 1993; Levi et al., 1993; Pethe et al., 2004; Rickards et al., 1994); still others have reported no consistent amplitude peak when tones were modulated at frequencies between 9 and 59 Hz (Stapells et al., 1988).

These investigations clearly demonstrate that ASSR amplitude in infants and young children are different from an adult. However, from this aggregate of information, it is difficult to extract any meaningful comparisons regarding modulation frequency, age-related amplitude changes, or conclusions regarding the maturation sequence of the ASSR for a number of reasons. Differences in stimuli, the age ranges of subjects (either too restricted or too broad), the ranges of modulation frequencies used, and the differences in the state of the subject during testing make it difficult to compare results across studies with any confidence. In addition, there is a paucity of information on the effect of modulation frequency on ASSR latency in infants and young children. Unfortunately, a literature search revealed only one study that partially addressed this issue (Cone-Wesson et al., 2002). Thus, both ASSR amplitude and latency functions are ill-defined in the early years of childhood.

In summary, while there has been substantial progress in understanding transient AEPs and their relation to the underlying mechanisms of ASSRs, there remain several areas that are largely uncharted and warrant investigation. In particular, ASSR amplitude and phase functions are not completely characterized across all transient AEPs in adults and are ill-defined in children. To a great extent, response measurements have been studied extensively and defined in adults at modulation frequencies greater than 10 Hz. However, few investigators have addressed

the response correlates at modulation frequencies lower than 10 Hz. In addition, the effects of repetition rate on response amplitude and latency are not defined in adults and children during sleep at very low modulation frequencies, lower than 10 Hz or correspondingly, the repetition rates characteristic of the LLR. Furthermore, specific changes in ASSR measurements have not been well characterized at different modulation frequencies in children.

The primary aim, therefore, of this study was to profile ASSR amplitudes in one particular age group of children and in adults over a wide range of repetition rates, specifically those that were expected to represent the general ranges of traditional AEPs. Figure 1 demonstrates what is expected, based on the literature review of transient AEPs, on the assumption of a general correspondence between latency of transient AEP components and periods of ASSR components (vis-à-vis modulation frequency). Striking is the disparity between response amplitudes between children and adults with stimulus repetition rates below 10 Hz. It was anticipated that such a difference could be demonstrated equally or more effectively taking a steady-state stimulus and analysis technique, with the advantage of objective response measurement and avoidance of subjective response interpretation.

Because specific changes in ASSR measurements are not well described in adults while asleep, the secondary aim of this study was an exploratory examination of the effect of repetition rate on response amplitude during natural sleep, to determine if results differ from those obtained when adults are awake.

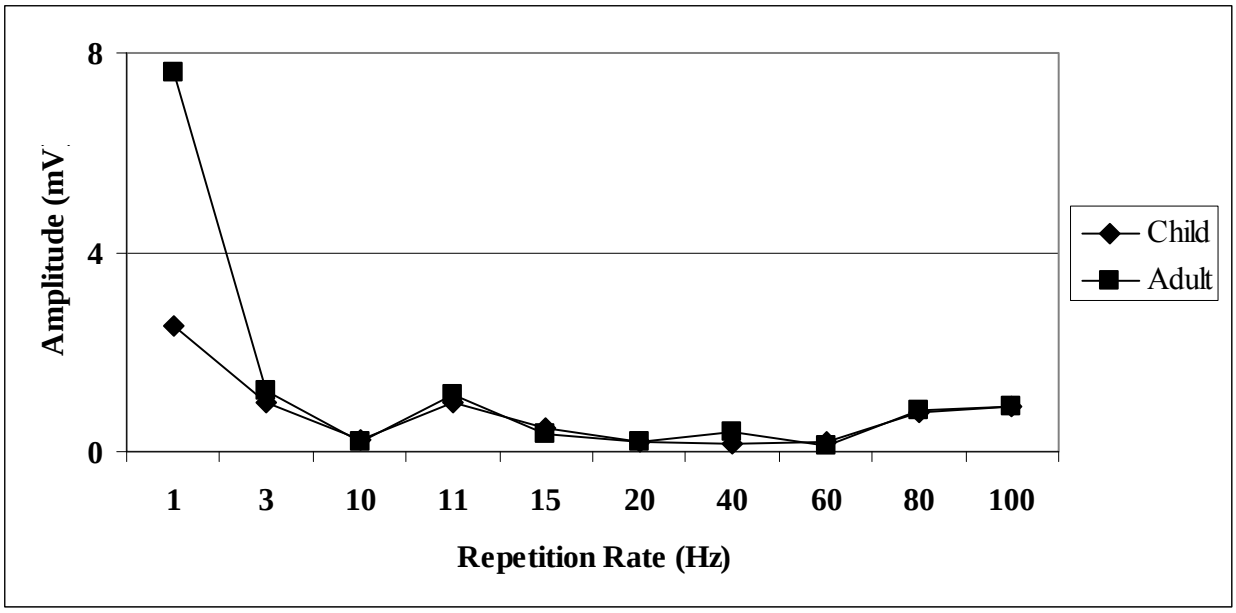


Figure 1 Summary of AEPS over a Wide Range of Repetition Rates

The last aim of this study was to examine the use of harmonic structure (Cebulla, Stürzebecher, & Elberling, 2006), to determine if it provides improved stability in response measurement, if not new insights. It is speculated that study profiles will provide valuable information that will advance the clinical application of ASSRs in deference to their importance to normal, abnormal or injured brain response development. Outcomes will also help to establish a foundation for future investigations regarding normal maturation and the potential to explore injured-brain function and investigations regarding neurologic disorders across levels of central auditory system.

2.0 STATEMENT OF THE PROBLEM

The transient-EP-analysis approach provides a broadly accepted way to identify and measure component AEPs. However, for purposes of looking across normal brain development, there is a need for a paradigm shift toward a process that objectifies AEP interpretation. The steady-state-analysis approach potentially provides a more analytical and objective approach whose advantages may well serve such interests as tracking maturational changes and/or effects of brain injury, that is, if the approach is extended to incorporate a more comprehensive representation of the AEP component waves. To investigate this possibility, the following specific aims will be pursued:

Specific Aim 1: Examine the effects of repetition (modulation) rate on ASSR amplitude in children and in adults to:

(a) Test between subject age-related amplitude values.

(b) Define the repetition rate(s) which evoke(s) maximal response amplitude as a function of age.

(c) Test-retest reliability.

Specific Aim 2: Explore the effects of repetition rate on response amplitude during sleep, to demonstrate if these effects differ from those obtained when subjects are awake.

Specific Aim 3: Examine the use of the fundamental as well as substantial higher harmonics, at each rate of repetition to determine if each analysis provides improved stability of response measurement.

3.0 REVIEW OF THE LITERATURE

3.1 AUDITORY EVOKED POTENTIALS

As previously mentioned, AEPs reflect electrical activity within the auditory system that is elicited by acoustic stimuli. The AEP metric represents a continuum of receptor and neurogenic potentials that are generated along the entire length of the auditory pathway. The most common classification of AEPs is based on their time domain; the time between the onset of the acoustic stimulus and the response (i.e., latency epoch). Chapter subsections are organized by the latency epoch that underscores each neurogenic potential generated along the peripheral and central auditory pathway (CAP). Each subsection offers a summary of the basic principles and clinical auditory applications of electrophysiological tests of the brainstem and CAP, as well as the effects of subject gender and ear dominance on AEP measurement.

3.1.1 Auditory Brainstem Response

The ABR is neurogenic potentials (I, II, III, IV, and V) elicited by transient stimuli that occur between 3 and 10 milliseconds (msec) following stimulus onset (Goldstein & Aldrich, 1999). By definition, the ABR follows the cochlear microphonic and precedes the middle latency response. The ABR represents a sequential series of replicable peaks and troughs reflecting synchronous activation of the distal portion of the auditory nerve up through rostral brainstem in response to

sound (Hall, J. W., III, 1992). Although the click ABR (c-ABR) is often considered to be more of a test of synchrony than of hearing *per se*, it possess excellent accuracy in indicating whether peripheral hearing is grossly intact for the high frequency portion of the speech range. The ABR provides a noninvasive measure that can be recorded in patients of all ages, including premature neonates, infants and in those whom it is difficult to assess auditory function through conventional audiologic testing. Responses are found to be virtually unaffected by state of consciousness such that recordings can be collected during natural sleep or sedation (Amadeo & Shagass, 1973; Osterhammel, Shallop, & Terkildsen, 1985; Picton, Hillyard, Krausz, & Galambos, 1974; Sohmer, Gafni, & Chisin, 1978).

The ABR is highly reliable in the normal auditory system, and shows predictable changes in waveform morphology to a variety of CNS disorders (e.g., acoustic tumors and demyelinating diseases) (Robinson & Rudge, 1975; Selters & Brackmann, 1977; Starr & Achor, 1975; Starr & Hamilton, 1976). The ABR is clinically defined by the latency of the response due to confounding variables, i.e., technical (e.g., electrode impedance) and biologic (e.g., resistance-capacitive properties of the skull) that contribute to the considerable inter- and intra-subject amplitude variability (Hecox & Burkard, 1982; Schwartz, Morris, & Jacobson, 1994; Silman & Silverman, 1991; Starr, Amlie, Martin, & Sanders, 1977). A strong sex and ear dominance affect appears to exist for the ABR. Data from past studies have shown that females have shorter latencies than males for later ABR waves, and latencies of left ears are shorter compared to those of the right (Beagley & Sheldrake, 1978; Chiarenza, D'Ambrosio, & Cazzullo, 1988; Jerger & Hall, 1980; Stockard, Stockard, & Sharbrough, 1978; Stockard, Stockard, Westmoreland, & Corfits, 1979).

3.1.2 Middle Latency Response

The MLR is neurogenic potentials (N_a, P_a, and N_b) elicited by transient stimuli that occur between 10 and 50 msec following stimulus onset (Geisler, Frishkopf, & Rosenblith, 1958). By definition, the MLR follows the ABR and precedes the long latency response. The MLR represents a sequential series of replicable peaks and troughs reflecting activation of cortical and subcortical generators of both primary and nonprimary auditory pathways in response to sound (Hall, J. W., III, 1992; McGee & Kraus, 1996; Møller, 1994). The MLR provides a noninvasive measure that can be recorded in patients of all ages, including premature neonates, infants and in those who cannot be evaluated adequately by conventional audiologic techniques. Responses obtained in adults are found to be virtually unaffected by state of consciousness such that recordings can be collected during natural sleep or sedation; whereas responses obtained in infants and young children are only intermittently obtained during certain stages of sleep (Kraus, Smith, Reed, Stein, & Cartee, 1985; Okitsu, 1984).

The MLR is highly reliable in assessing auditory pathway function (e.g., auditory brainstem abnormalities when the ABR is absent and cortical lesions affecting the temporal lobe) and in predicting low frequency hearing sensitivity in adults, and in young children when sleep stage is monitored (Kileny, Paccioretti, & Wilson, 1987; Kraus, McGee, & Stein, 1994; Kraus, Özdamar, Hier, & Stein, 1982). The MLR is clinically defined by the amplitude of its response for a number of reasons. The MLR is composed of somewhat lower-frequency energy (thus precise latency resolution is less important), has considerable inter-subject latency variability, and latency appears to be a less sensitive indicator of pathology than is response amplitude (Kileny et al., 1987; Kraus et al., 1982). Results of earlier research, such as that of Kraus and

colleagues (1985) revealed no significant differences in MLR detectability in males versus females and right versus left ear.

3.1.3 Long Latency Response

The LLR is neurogenic potentials (P_1, N_1, P_2, and N_2) elicited by transient and speech stimuli that occur between 50 and 250 msec following stimulus onset (Davis & Zerlin, 1966). By definition, the LLR is an exogenous response that follows the MLR and precedes auditory event-related potentials. The LLR comprises a sequential series of replicable peaks and troughs reflecting activation mainly within the primary and secondary auditory cortex (midline and lateral temporal surface, respectively) in response to sound (reviewed by Steinschneider and Dunn, 2002). The LLR provides a noninvasive measure that can be recorded in alert patients of all ages, including premature neonates and infants. Responses obtained in both children and adults are affected by state of consciousness such that natural sleep, sedation and attention to the stimulus have a pronounced effect on LLR waveforms (Cody, Klass & Bickford, 1967; Davis, 1964; Weitzman & Kremen, 1965; Williams, Tepas, & Morlock, 1962).

In addition to estimating auditory sensitivity, the LLR is reliable in passively cooperative, alert subjects in assessing auditory pathway function (e.g., identifying brain lesions and localizing brain dysfunction), measurement of temporal discrimination, localization, and speech perception (reviewed by Curry, Woods, & Low, 1986; Hyde, 1994; Kileny & Berry, 1983). The LLR analysis and clinical interpretation is not as clearly defined as the ABR or the MLR, but is typically described in terms of both the amplitude and the latency of its response. A strong sex effect appears to exist for the LLR, with females showing larger amplitudes than males

(Buchsbaum, Henkin, & Christiansen, 1974; Camposano & Lolas, 1992). There is no available evidence that suggest LLR differences for right versus left ear.

3.1.4 Auditory Steady-State Response

The ASSR is neurogenic potentials that are elicited traditionally by modulated tones. The ASSR is believed to be a composite of transient components generated by the activation of the pontine brainstem (presumably in common with production of the auditory brainstem response [ABR]) and higher central auditory pathways perhaps to the level of radiations to the primary cortex (presumably in common with production of the middle-latency response [MLR]) (Herdman et al., 2002; Kuwada et al., 2002). The steady-state response reflects the overlapping continuum of neural discharge, which closely follows the time course of the modulation frequency. Stimuli are presented at a high enough modulation frequency that the brain and subsequent auditory structures do not settle down to their undisturbed state, and their evoked responses do not die away between each subsequent stimulus presentation. Thus, evoked responses overlap at the frequency of modulation which makes the synchronization of neural firing less critical for a response. When analyzed over time the ASSR presents a sinusoidal waveform, and when displayed in frequency it exhibits a prominent single spectral component corresponding to the frequency of modulation.

The ASSR provides a noninvasive measure that permits estimations of hearing sensitivity in the mid-to-upper audiometric frequencies (e.g., 1 and 2 kHz, perhaps even 4 kHz) across all age groups (Kaf, 2003; Lins et al., 1996; Perez-Abalo et al., 2001; Rance, Rickards, Cohen, De Vidi, & Clark, 1995). The ASSR can provide reasonably accurate estimations of behavioral hearing thresholds in both normally hearing and hearing-impaired individuals. However, there

are discrepant findings as to whether the ASSR differentiates between elevated thresholds associated with peripheral versus auditory dysfunction (e.g., auditory neuropathy, auditory processing disorder) or retrocochlear abnormalities (Rance et al., 1999; Rance et al., 2005; Shinn & Musiek, 2007). In contrast, at suprathreshold levels the component synchrony measure (CSM, also known as PC^2) was found to be useful for detecting desynchronization of the 40-Hz ASSR in patients with CNS disorders (Harada, Aoyagi, Suzuki, Kiren, & Koike, 1994). The ASSR is not appreciably affected by subject-related variables such as natural sleep or sedation when using modulation frequencies in excess of 60 Hz (Aoyagi et al., 1994; Aoyagi et al., 1993; Cohen et al., 1991; Levi et al., 1993; Lins & Picton, 1995; Rickards et al., 1994). The ASSR is usually characterized by both amplitude and phase. However, because of the ambiguities inherent in circular measurement (Fisher, 1993; John & Picton, 2000b), phase may be expressed in terms of apparent (Regan, 1966) or derived (Diamond, 1977a, 1977b) latency, which is measured in msec. A sex affect appears to exist for the ASSR in that females show slightly larger (11%) and slightly earlier (0.10 to 0.78 msec) latencies compared to males (John & Picton, 2000b; Picton, van Roon, & John 2009). However, no consistent ear-related asymmetry or effects of handedness have been found on ASSR threshold measures (Lins et al., 1996; Perez-Abalo et al., 2001; Picton et al., 2009).

In summary, AEPs occur as a sequential series of peaks and troughs that are generated from all levels of the auditory system. These potentials reflect activity from multiple contributing sources, which tend to become more complex the later the potential occurs in time. Auditory evoked potentials elicited by transient and steady-state stimuli provide a noninvasive measure that can be recorded in patients of all ages, including premature neonates, infants and in those who cannot be evaluated adequately by conventional audiologic techniques. Most

responses obtained in adults are found to be virtually unaffected by state of consciousness such that recordings can be collected during natural sleep or sedation. However, numerous studies have demonstrated that the MLR and LLR are obtained inconsistently in infants and young children during certain stages of sleep (cf. Subsection 3.6). Transient and steady-state AEPs are fairly analogous in estimating hearing sensitivity, however diagnostically they differ. While it is clear from the literature that transient AEPs have been extensively evaluated in patients with neurologic disorders, the association between steady-state AEPs and the diagnosis of neurologic disorders need to be further evaluated. A strong sex affect appears to exist, with females showing shorter latencies and larger amplitudes than males for the ABR, ASSR and the LLR.

3.2 DEVELOPMENT OF THE PHERIPHERAL AUDITORY SYSTEM

The peripheral auditory system consists of three major portions of the ear: the outer (OE), middle (ME) and inner ear (IE). Because the auditory system appears to develop simultaneously from the ME to the auditory cortex, chapter subsections are limited to the development of the ME and the cochlea of the IE. The OE, with the exception of some salient features and the vestibular system of the IE are not included. Although the neuroanatomical data of the middle and IE does not contribute specifically to the hypotheses or methods of this dissertation study, it provides a broad framework within which the growth of auditory response measurements is contingent upon. It is not the purpose of this subsection to comprehensively review all the literature and all aspects of morphological development of the peripheral auditory system; other reviews are available to the reader, in particular, Bredberg (1968), Rubel (1978) and van De Water (1983).

This chapter subsection will introduce, rather, the functional roles and the structural events involved in human neuroanatomical development of the ME and the cochlea of the IE.

3.2.1 Middle Ear

The ME is an air-filled cavity lined with a mucous membrane, which mechanically links the air-filled OE and the fluid-filled IE via the auditory ossicles. Because of the difference in impedance of air and water, the ME acts as an acoustical transformer by compensating for much of the impedance mismatch that would result if airborne sound waves impinged directly on the fluid-filled cochlea. Thus, the areal ratio of the tympanic membrane to the stapes footplate and the lever system that exists within the ossicles significantly reduces the reflection of sound energy that would otherwise occur when sound waves from the OE are transmitted from the stapes footplate in the oval window to the sensory epithelium in the cochlea.

The earliest embryological sign of the development of the ME is the primitive formation of the tympanic cavity and the eustachian tube (i.e., turbotympanic recess) from the dorsal recess of the first (and possibly the second) endodermal pharyngeal pouch (Frazer, 1914; Hammer, 1902; Wong, 1983). The turbotympanic recess starts its development in the third to fourth week of fetal development. The first and second branchial arches constitute the anlage for the auditory ossicles, muscles, tendons and connective tissues. Moreover, at this early developmental stage the nerves of the first and second branchial arches--the trigeminal and facial nerves respectively--are connected through the chorda tympani (Altmann, 1950). The auditory ossicles appear in the sixth week gestational age (GA), with the malleus and incus visible within the mesenchyme of the first and second branchial arches, and the stapes at the end of the second visceral bar. In the eighth week GA, the endoderm of the turbotympanic recess comes in contact with the

ectodermal membrane of the first branchial groove. The positioning of these epithelia is brief, since connective tissue grows between them which later condense to form the trilaminar tympanic membrane. Within this connective tissue is a mass of condensed mesenchyme which is the primordia of the manubrium of the malleus (Anson & Donaldson, 1981; Bast & Anson, 1949; Pearson, Jacobson, Van Calcar, & Sauter, 1973). Shortly after the eighth week GA, the proximal part of the pharyngeal pouch constricts to form the eustachian tube, and the distal end widens to form the tympanic cavity proper. In the 10th week GA, the future of the external auditory meatus becomes apparent when the terminal end of the entodermal pouch flattens against the ectoderm of the invaginating first branchial groove (Altmann, 1950; Anson & Donaldson, 1981; Pearson et al, 1973). In the same week the pars tensa of the tympanic membrane becomes visible (Altmann, 1950).

As the growth and transformation of the tympanic cavity continues, the formation of the tegman tympani occurs from the petrous portion of the temporal bone. During the following week the anlage of the stapedius muscle becomes defined from the dense mesenchyme lateral to the cochlea, while the tensor tympani muscle is actualized slightly later in the 13th week GA (Altmann, 1950). Although just a sulcate impression on the wall of the otic otocyst (cf. Subsection 3.2.2), the facial canal which already houses the facial nerve, the stapedius muscle and blood vessels that supply the tympanic cavity is realized in the 12th week GA (Anson & Donaldson, 1981; Bast & Anson, 1949; Pearson et al., 1973). In the same week, the incus approaches the stapes, and the stapes applies itself closely to the otic otocyst. During this time, the malleus and incus as well as the otic otocyst begin to change to precartilage. In the 13th week GA, the stapes is pressed into the lateral wall of the otic otocyst. Shortly after, the stapes and the otic otocyst begin to undergo a similar change to true cartilage (Bast & Anson, 1949). By the

16th week GA, all the ossicles have attained maximum size and have clear adult morphology. At this time, bone formation is initiated in the malleus and incus, and three weeks later, by the 19th week GA the initial step in ossification begins in the stapes (Altmann, 1950; Anson & Donaldson, 1981; Pearson et al., 1973). Shortly after, just one week later the pars flaccida of the tympanic membrane is visible (Altmann, 1950). During this same time, the insertion of the tendons of the tensor tympani muscle (onto the malleus) and stapedius muscle (onto the stapes) occur (Saunders, Kaltenbach, & Relkin, 1983). From the 18th to the 21st week GA, mesenchyme tissue in the tympanic cavity transforms to myxomatous (i.e., mucoid) tissue, which extends into the epitympanic recess. By the 23rd week GA, the anterior and part of the lateral wall of the tympanic cavity develop from the squamous portion of the temporal bone. Moreover, the pneumatic space behind the epitympanic recess opens to form the tympanic antrum, and, the ossification of the tegman tympani begins (Bast & Anson, 1949; Pearson et al., 1973; Wong, 1983).

As development proceeds, a posterior mesentery-like fold is realized in the medial wall of the tympanic cavity, which forms the round window, tympanic sinus, and a large part of the oval window. Concurrently, the tympanic cavity widens and its mucoid lining envelops the ossicles, tensor tympani, and the chorda tympani in the 25th week GA (Pearson et al., 1973). By the 28th week GA the mucoid tissue of the tympanic cavity is fully absorbed. Shortly after, pneumatization of the temporal bone occurs, and the deposition of the petrous and mastoid bones continues through childhood (Anson & Donaldson, 1981; Bast & Forester, 1939; Pearson et al., 1973). In the 29th week GA, pneumatization of the epitympanic recess lags behind that of the tympanic cavity; however, both are virtually complete by the 36th week GA (Bast & Anson, 1949). The tympanic space, albeit continues to enlarge in postnatal life until adolescence (Eby &

Nadol, 1986; Pearson, 1973). Ossification of the malleus, incus, and stapes are complete by the 32nd week GA; however, pneumatization of the ossicles may continue until adulthood (Anson & Donaldson, 1981; Eby & Nadol, 1986; Wong, 1983).

By the 40th week GA, the formation of the tympanic membrane is fully developed and lies nearly parallel to the walls of the external auditory canal. After birth, the lower wall of the canal comes in contact and begins to fuse with the adjacent walls of the canal (Pearson, 1973). After the second year of life, the bony portions of the external auditory canal become completely osseous (Pearson, 1973). It is during this same time, the tympanic membrane assumes are more conical shape and its plane changes its relative position to take a more vertical orientation which becomes adult-like by three years of age (Ikui, Sando, Sudo, & Fujita, 1997; Pearson, 1973).

3.2.2 Inner Ear

The cochlea is a conical cavity in the petrous portion of the temporal bone which contains the organ of Corti. The role of the cochlea is not limited to the transduction of fluid vibrations into nerve impulses; it also includes the frequency analysis of these vibrations before they are transmitted to the central auditory structures. Fluid vibrations in the cochlea are initiated by the movement of the stapes footplate in the oval window. These vibrations activate the release of neurotransmitter into the synaptic clefts at the base of the hair cells, which propagate auditory nerve impulses. The frequency analysis of these fluid vibrations is related to the mechanical properties (i.e., the stiffness gradient) of the basilar membrane (BM), and the active metabolic mechanisms of the outer hair cells (OHCs), both of which help to optimally activate different frequency regions of the BM.

The earliest embryological sign of the development of the cochlea is the thickening of the cephalic ectoderm--the otic placode. The otic placode invaginates into the mesenchymal tissue by the fourth week of fetal development to form the otic pit. As the invaginated portion of the otic pit enlarges, the mouth narrows until the two sides merge forming a closed sac--the otic otocyst (Altmann, 1950; Bast & Anson, 1949; O'Rahilly, 1963; Wong, 1983). The epithelium of the otic otocyst gives rise to the primary neurons of the vestibulocochlear ganglion. These ganglions later divide into superior (i.e., vestibular ganglion supplying the common macula) and inferior (i.e., spiral ganglion supplying sensory hair cells) branches (Pearson, et al., 1973) late in the fourth or early in the fifth week GA. After invagination, the otic otocyst divides into the endolymphatic duct and sac, the utricle, semicircular canals and the saccule, as well as the cochlear duct (Altmann, 1950; Bast & Anson, 1949; Bredberg, 1968; Pearson et al., 1973; Wong, 1983). Thus, by the six week GA the sensory epithelium of the otic otocyst divides into vestibular and cochlear regions, into which terminal nerve fibers from the vestibulocochlear ganglia will grow.

While various changes are taking place in the otic otocyst, the mesoderm surrounding it is also undergoing development. Consequently, toward the end of the sixth week GA, the condensed mesenchyme tissue completes its transformation to cartilage at the peripheral areas of the developing otic otocyst. During the course of the next two weeks the organ of Corti develops in the wall of the cochlear duct, its inner ridge (later known as the spiral limbus) and outer ridge (later differentiates into the organ of Corti) are already noticeable. Both ridges secrete a jelly-like substance forming the nascent tectorial membrane. A highly vascularized band of cells (stria vascularis) begins to develop on the outer wall of the cochlear duct in the eighth week GA. Just one week later, nerve fibers from the spiral ganglion are seen entering the epithelium below

the posterior wall (i.e., BM) of the cochlear duct (Pearson et al., 1973; Pujol & Lavigne-Rebillard, 1985; Wong, 1983). Late in the seventh week GA the cochlear duct completes one turn around the modiolus, and continues to course spirally around the modiolus two and one half turns by the ninth week GA (Pearson et al., 1973; Pujol & Lavigne-Rebillard, 1985). The developing tectorial membrane covered in the organ of Corti's primordium is detected by the 10th week GA (Pujol, Lavigne-Rebillard, & Uziel, 1991).

As morphological development of the otic otocyst proceeds, the epithelium covering the BM starts to exhibit signs of maturation beginning in the basal end proceeding gradually toward the apex. Afferent nerve fibers begin to invade the undifferentiated cochlear epithelium--with a slight developmental precedence of inner hair cells (IHCs) over that of OHCs (Anson & Donaldson, 1981; Bast & Anson, 1949; Bredberg, Engstrom, & Ades, 1965; Bredberg, 1967, 1968; Lavigne-Rebillard & Pujol, 1986, 1988). In the 11th week GA, the cochlear duct (i.e., scala media) begins to differentiate. Perilymphatic spaces begin to change the cross-sectional form of the cochlear duct from rounded to triangular--the posterior wall formed by the BM, the anterior wall by the vestibular (Reissner's) membrane, and the outer wall formed by the spiral ligament and the bony lamina--separating the three spirally-running scalae which communicate at the apex of the cochlea (Anson & Donaldson, 1981; Bast & Anson, 1949; Bredberg, 1968).

Subsequently, the differentiation of stereocilia bundles begins on the IHCs first, then the OHCs in the 12th week GA. The first vesiculated efferent endings are visible below the IHCs in the 14th week, contrasting with the late arrival of synapses between the medial efferent endings and the OHCs around the 20th week GA (Lavigne-Rebillard & Pujol, 1988; Pujol & Lavigne-Rebillard, 1985). All rows of inner and OHCs are apparent by the 14th week

GA and their characteristic arrangement of stereocilia is seen around the 22nd week GA (Lavigne-Rebillard & Pujol, 1986, 1988; Pujol & Lavigne-Rebillard, 1985; Pujol et al., 1991). As soon as the staircase arrangement of stereocilia becomes clear, tip links are present on most of the hair cells (Lavigne-Rebillard & Pujol, 1986). By the 16th week GA auditory nerve fibers are present in all turns of the cochlea and are tonotopically distributed; the center contains nerve fibers arising from the apex and the outer covering contains nerve fibers from progressively more basal regions of the cochlea (Rubel, 1978). Between the 20th and the 22nd week GA, the inner and outer ridges from the epithelial cells of the scala media form the spiral limbus and the organ of Corti, respectively. At the same time, the stria vascularis is well developed forming a thick covering over the entire outer wall (Bredberg, 1968). Simultaneously appearing is the opening of the tunnel of Corti, the formation of Nuel's spaces, the elongation of the outer pillars, and the development of divergent cell types (i.e., Deiters' cells, Hensen's cells) (Altmann, 1950; Lavigne-Rebillard & Pujol, 1986, 1988; Pujol & Lavigne-Rebillard, 1985).

By the 23rd week GA all the ossification centers of the otic otocyst have fused to form a completely bony capsule. Just one week later, the organ of Corti is present in all turns of the cochlea, and the last stages regarding the formation of synapses, as well as the formation of cilia are almost complete (Pujol & Lavigne-Rebillard, 1985). Functional maturation of the cochlea is attained by the 25th week GA (Anson & Donaldson, 1981; Bast & Anson, 1949). Outer HCs, Deiters' cells and other surrounding cochlear structures reach maturity slightly after the onset of cochlear function, by the 30th week GA (Lavigne-Rebillard & Pujol, 1990; Pujol & Uziel, 1988).

In summary, the myriad of structural events that synchronously occur prenatally, harmoniously contribute to the formation and onset of auditory function (cf. Table 1). Even though, anatomic maturity of the ME and the cochlea of the IE is not completely attained

prenatally, unconditional fetal auditory responsiveness (e.g., limb and body movements, heart rate and eye blink) occurs as early as the 25th week GA (Birnholz & Benacerraf, 1983; Crade & Lovett, 1988; Johansson, Wedenberg, & Westin, 1963), and reliable components of evoked potentials can be successfully recorded around the 27th week GA (Galambos & Hecox, 1978; Rotteveel, de Graaf, Colon, Stegeman, & Visco, 1987a; Starr et al., 1977).

While this chapter subsection addressed the development of the peripheral auditory structures, subsection 3.3 will detail the functional roles and salient points involving human formation and growth of the central auditory system.

Table 1 Embryonic Development of the Peripheral Auditory System

GA[a]	Middle Ear	Inner ear
3rd	Marks the start of the primitive formation of the tympanic cavity and eustachian tube, and the anlage for the auditory ossicles, muscles, tendons and connective tissues. Trigeminal and facial nerves connect through the chorda tympani.	
4		The otic placode invaginates to form the otic otocyst.
5		The vestibulocochlear ganglion divides into superior and inferior branches and the sensory epithelium of the otic otocyst divides onto the vestibular and cochlear regions.
6	The auditory ossicles are visible.	The peripheral areas of the otic otocyst transform to cartilage. Marks the beginning of the formation of the organ or Corti, the spiral limbus and the tectorial membrane.
7		The cochlear duct completes one turn around the modiolus.
8	The primordium of the manubrium of the malleus becomes defined.	The stria vascularis begins to develop on the outer wall of the cochlear duct.
9	Condensed connective tissue forms the tympanic membrane. The eustachian tube and the tympanic cavity proper are realized.	Nerve fibers from the spiral ganglion enter the epithelium below BM. The cochlear duct completes two and one half turns around the modiolus.
10	The external auditory meatus becomes apparent and the formation of the tegman tympani occurs. In the same week the pars tensa of the tympanic membrane becomes visible.	The developing tectorial membrane is detected. The epithelium covering the BM starts to mature basal-to-apex. Afferent nerve fibers being to invade the cochlear epithelium, first the IHC then the OHCs.
11	The anlage of the stapedius muscle becomes defined.	The cochlear duct begins to differentiate.
12	The facial canal is realized. The malleus and the incus begin to change to precartilage.	Differentiation of stereocilia bundles begins on the IHCs then the OHCs.
13	The tensor tympani is actualized.	
14	The stapes begins to change to true cartilage.	Efferent endings are visible below the IHCs. All rows of inner and OHCs are apparent.

Table 1 continued.

16	Ossicles have attained maximum size. Bone formation is initiated in the malleus and incus.	Nerve fibers are present in all turns of the cochlea and are tonotopically distributed.
19	Ossification begins in the stapes.	
20	The pars flaccida of the tympanic membrane becomes visible.	Synapses between the medial efferent endings and the OHCs are apparent.
21		The spiral limbus and the organ of Corti form. The stria vascularis is well developed. The opening of the tunnel of Corti, the formation of Nuel's spaces, the elongation of the outer pillars, and the development of divergent cells types start to appear.
22		Staircase arrangement of stereocilia becomes clear and tip links are present.
23	The anterior and lateral walls of the tympanic cavity develop and the tympanic antrum forms. The tegman tympani start to ossify.	All ossification centers have fused to form a completely bony capsule.
24		The organ of Corti is present on all turns of the cochlea. The formation of cilia is almost complete.
25	The round window, tympanic sinus and a large part of the oval window form. Tympanic cavity widens.	Functional maturation of the cochlea and unconditional fetal auditory responsiveness is attained.
27		Reliable components of AEPs can be successfully recorded.
28	Pneumatization of the temporal bone occurs; the deposition of the petrous and mastoid bones continues through childhood.	
29	Pneumatization of the epitympanic recess and the tympanic cavity occurs.	
30		Outer HCs, Deiters' cells and other surrounding cochlear structures reach maturity.
32	Ossification of the malleus and incus is complete; stapes continues until adulthood.	
36	The epitympanic recess and the tympanic cavity are pneumatized.	
40	The formation of the tympanic membrane is fully developed.	

Note: [a] Weeks of gestation.

3.3 DEVELOPMENT OF THE CENTRAL AUDITORY SYSTEM

The central auditory pathway (CAP) is not only a collection of nuclei and interconnecting fiber tracts, but also relay and processing centers that analyze, code and transmits auditory signals from the ear to the primary auditory cortex. The chapter subsections are arranged to represent the structural bases for processing auditory information. Because this dissertation study was not designed to obtain human neuroanatomical data, the evidence presented does not contribute specifically to the study hypotheses and methods; however, it is included to introduce the reader to the complexities underlying the development of the CAP. Other reviews are available to the reader which analyzes these embryological aspects in more detail using different species, namely, Rubel (1978) and Cant (1998).

3.3.1 Cochlear Nucleus

The cochlear nucleus (CN) receives, transforms and relays information encoded in auditory nerve fiber discharge patterns to higher centers of the auditory pathway. The CN includes second-order neurons and is divisible into the dorsal cochlear nucleus (DCN), the anterior ventral cochlear nucleus (AVCN), and the posterior ventral cochlear nucleus (PVCN). These divisions are based on the morphology of the cell types they contain (i.e., octopus, bushy and spindle) and the structures with which they connect along the auditory pathway (Brawer, Morest, & Kane, 1974). Because each division of cochlear nuclei has a unique combination of cell types their growth over time is dependent on their size and morphology. All three cochlear nuclei are tonotopically arranged--with low frequencies represented ventrolaterally and high frequencies represented dorsomedially (Sando, 1965). The auditory pathway diverges into multiple parallel

tracts as it leaves the CN. While the auditory nerve connects almost exclusively with the CN, the CN divides its input into several different ascending tracts.

In early embryonic life, late in the sixth or early in the seventh week GA, neurons of the rhombic lip form the CN (Bayer, Altman, Russo, & Zhang, 1995; Cant, 1998; Willard, 1995). Just one week later, the cochlear root is present in the medulla, and differentiation of first and second-order neurons appears to occur simultaneously (Rubel, 1978). By the 16th week GA cochlear nerve fibers innervate the cochlear nuclei of the brainstem (Rubel & Fritzsch, 2002). Linear arrays of oligodendroctyes and faint myelin sheaths on the axons in the CN are visualized by the 26th week GA. The density of myelination increases steadily from the 29th week GA to term (i.e., 40 to 44 weeks GA) (Moore, Perazzo, & Braun, 1995; Yakovlev & Lecours, 1967), and approximates that of an adult state 1 year postnatal age (Moore et al., 1995). By the 30th week GA, CN morphology is similar to that of an adult. In addition most growth of the CN--cell bodies, dendrites, and the growth of axons and myelin sheaths of auditory nerve fibers--occurs before the seventh postnatal week (Brugge, 1983).

3.3.2 Superior Olivary Complex

The superior olivary complex (SOC) contains third-order neurons that receive and integrate information arising from both the ipsilateral and contralateral CN. In addition to relaying information from the CN to higher auditory centers, the SOC contains olivocochlear neurons which are primarily associated with the efferent auditory system. The SOC is composed of the lateral and medial nuclei of the superior olive (LSO and MSO), and the medial nucleus of the trapezoid body (MNTB). Periolivary nuclei are also identified, however they are usually found scattered around the LSO and MSO. Nuclei are based on the different anatomic and functional

input types that cells in these regions receive. While most neurons of the MSO are excited by stimulation of either ear, the LSO receives excitatory input only from the ipsilateral ear, and the MNTB only receives excitatory input from the contralateral ear. Interaural delays are examined by horizontal time differences in the MSO analyzing low frequencies, and horizontal intensity differences in the LSO and MNTB analyzing high frequencies. Similar to that of the CN, all groups of nuclei of the SOC have tonotopic organization. In the LSO and MNTB, the low frequencies are lateral and the high frequencies are positioned medially (Tsuchitani & Boudreau, 1966); whereas, in the MSO the low frequencies are dorsal and the high frequencies are positioned ventrally (Brugge & Geisler, 1978). The SOC receives input from the AVCN and the axons of both the MSO and LSO extend and contribute to the lateral lemniscus, which carries information to the midbrain.

There is very little information available regarding the human development of the SOC in early embryonic life. In general the neuroepithelial source(s) of the SOC are not clear; however their nuclei are apparent in the eighth week GA (Streeter, 1912). Neurons of the SOC are thought to generate from the dorsal aspect of the medullary epithelium and possibly from a portion of the rhombic lip, and then migrate ventrally to their final location (Altman & Bayer, 1980; Nornes & Morita, 1979). Linear arrays of oligodendroctyes and faint myelin sheaths on the axons in the SOC are observed by the 26th week GA. The density of myelination increases steadily from the 29th week GA to term (Moore, et al, 1995; Yakovlev & Lecours, 1967), and approximates that of an adult state one year postnatal age (Moore, et al., 1995).

3.3.3 Lateral Lemniscus

The lateral lemniscus (LL) is the largest tract of the auditory brainstem--composed of both afferent and efferent auditory nerve fibers--that carries information to the inferior colliculus in the midbrain. The LL carries fibers whose soma reside in several different structures, e.g., AVCN, PVCN, DCN, MSO and LSO, and enter the LL via parallel routes. The LL also contains interstitial nuclei referred to as the ventral and dorsal nuclei of the LL (NLL), and the intermediate nucleus of the LL. Only some of the axons traveling in the LL synapse in either of these nuclei. Most continue directly to their destination in the inferior colliculus, the medial geniculate body or to other more rostral regions of the brain. The LL has a high degree of tonotopic organization (Brugge & Geisler, 1978), such that the high frequencies are ventral and the low frequencies are arranged dorsally (Aitkin, Anderson, & Brugge, 1969).

Like the SOC, there is very little information available regarding the human development of the LL in early embryonic life. In general, the neurons of the LL are thought to generate as early as, or earlier than neurons of the CN, and develop and proliferate during the same time period as the SOC (Cant, 1998). However, the ventral and dorsal interstitial nuclei are known to originate sequentially mainly during the fourth week to the middle of the seventh week GA (Bayer et al., 1995). Linear arrays of oligodendroctyes and faint myelin sheaths on the axons in the LL are evident by the 26th week GA (Moore, et al., 1995; Yakovlev & Lecours, 1967; also Inagaki et al., 1987, who estimates about the 28th week GA). The density of myelination increases steadily from the 29th week GA to term (Inagaki et al., 1987; Moore, et al., 1995; Yakovlev & Lecours, 1967), and approximates that of an adult state one year postnatal age (Moore, et al., 1995).

3.3.4 Inferior Colliculus

The inferior colliculus (IC) serves as an obligatory relay center for all of the afferent and efferent auditory fibers. It is in this portion of the auditory pathway that the third-order neurons terminate. The IC receives most of its input from the LL and projects axons ipsilaterally via the brachium of the IC to the medial geniculate body. The IC is divisible into three morphologically distinct nuclei. The largest and most well studied of these is the central nucleus (CNIC). The remaining portions of the IC have been divided into the external nucleus and the pericentral nucleus (Berman, 1968; Rose, Greenwood, Goldberg, & Hind, 1963). Maturation of these cell types is dependent on their size and morphology; neurons in the IC will grow and differentiate faster than those in the external nucleus (Morest, 1969). Neurons of the IC are sensitive to time and spatial localization (Knudson & Konishi, 1978), as well as binaural stimulation (Benevento & Coleman, 1970). The IC has a high degree of tonotopic organization, such that the high frequencies are ventral and the low frequencies are arranged dorsally (Merzenich & Reid, 1974).

In early embryonic life the neurons of the IC develop from the neuroepithelial cells of the posterior recess of the cerebral aqueduct (Altman & Bayer, 1981; Bayer et al., 1995; Cooper & Rakic, 1981). Generation starts from the sixth and continues until the 17th week GA. In the eighth week GA (O'Rahilly & Gardner, 1971; also Cooper 1948, who estimates about the 12th week GA) the IC is considered recognizable. Linear arrays of oligodendroctyes and faint myelin sheaths on the axons in the IC are evident by the 26th week GA. The density of myelination increases steadily from the 29th week GA to term (Moore, et al., 1995; Yakovlev & Lecours, 1967), and approximates that of an adult state one year postnatal age (Moore, et al., 1995).

3.3.5 Medial Geniculate Body

The thalamus is the last relay site on the way to the cortex for almost all sensory information, including auditory, visual, and somatosensory. The medial geniculate body (MGB) is the auditory nucleus of the thalamus that receives primary afferent fibers from the IC via the brachium of the IC and sends fibers to the auditory cortex. The MGB is divisible into ventral, medial, and dorsal subnuclei. These divisions are based on functional as well as morphological distinctions. The ventral division contains fourth-order neurons that relay detailed auditory information to the primary auditory cortex, whereas the dorsal division sends auditory attention information to associated auditory cortices, and the medial division projects multimodal arousal information (e.g., vestibular, somesthetic, and visual) to both auditory and non-auditory cortices of the forebrain (Winer, 1984, 1985). Maturation of these cell types is dependent on their size and morphology; principle neurons in the ventral nucleus grow and differentiate faster than those in the dorsal nucleus (Morest, 1969). Only the ventral division of the MGB has a high degree of tonotopic organization, such that low frequencies are positioned laterally and high frequencies are positioned medially (Aitkin & Webster, 1972). Auditory information from all three divisions enters the cerebral cortex via the sublenticular portion of the internal capsule.

In early embryonic life neurons of the MGB develop from the dorsal neuroepithelial cells of the third ventricle in the posteroventral thalamus (Altman & Bayer 1979, 1989). Generation starts from late in the fifth week to late in the sixth week GA (Cooper, 1948). Starting at the end of the sixth week GA the MGB is displaced and begins to migrate until the eighth week GA (Bayer et al., 1995; Cooper, 1948; and Dekaban, 1954 who places migration a little later, between the 11th and 21st week GA). Cell differentiation begins in the 21st week GA, and by term the MGB is seen in its final shape and location (Dekaban, 1954). Myelination begins in the

28th week GA--which is among the earliest thalamic fibers to become myelinated--and is complete at about the fourth postnatal month (Yakovlev & Lecours, 1967).

3.3.6 Reticular Formation

Although the reticular formation is intricately connected to the auditory system, it is not always recognized as a major part of the traditional CAP. However, because the ascending reticular activating system (ARAS) is heavily involved in states of arousal, it is an important component in evoking electrophysiological responses, and thus its structure and function will be discussed briefly.

The reticular formation is a set of interconnected nuclei that form the central core of brainstem, running though the middle of the medulla and pons on into the midbrain. This core network of nuclei has both ascending and descending tracts on each side of the brainstem. The reticular formation is divisible into the nuclei of the raphe, the paramedian reticular nuclei, and into the medial and lateral regions. Because of the large number of collateral fibers projected to the lateral region from various surrounding sensory systems (e.g., auditory and vestibular), this region is regarded as the ARAS. The effect of impulses from various sensory systems terminating in the lateral region plays an important role in wakefulness, alerting and arousal. The ARAS is sensitive to certain drugs including tranquilizers and general anesthetics. This sensory part of the reticular system projects to the intralaminar and midline nuclei of the thalamus--which are also believed to play a role in wakefulness--after which information is sent to the cortex (Carpenter & Sutin, 1983).

There is very little information available regarding the human development of the ARAS in early embryonic life. Neurons generated in the medullary reticular formation generate from

the fourth to the seventh week GA (Bayer et al., 1995). At term the reticular formation is almost devoid of myelinated fibers. The cycle of myelination in the reticular formation is very slow--only incipient myelination is present at one year postnatal age--extending until the age of puberty (Yakovlev & Lecours, 1967).

3.3.7 Auditory Cortex

Neurons originating in the MGB radiate to the auditory areas of the cerebral cortex completing the ascending auditory system. The cerebral cortex consists of six horizontal cell layers (I molecular; II external granular; III external pyramidal; IV internal granular; V internal pyramidal; VI multiform) which can be distinguished by the cell type, density, and arrangement (Carpenter & Sutin, 1983). Cells responsive to acoustic stimuli exist in all cell layers, except layer I. Sensory inputs first activate neurons in layer IV, which propagate the excitement up to layers II and III, and from there down to layers V and VI.

Brodmann areas 41 and 42 mark the location of the primary auditory cortex which is the cortical region responsible for the sensation of sound. The primary area is buried in the floor of the lateral sulcus (i.e., sylvian fissure). The principle auditory receptive area (41) is located in the middle part of the anterior transverse gyrus (i.e., Heschl's). The remaining parts of Heschl's gyrus and adjacent portions of the sylvian fissure, compose area 42, which is largely an auditory association area. Each receptive area is thought to process different aspects of the acoustic stimuli (e.g., processing complex sounds and discrimination of timing and temporal patterns). As in the brainstem, distinct tonotopic organization exists in area 41 with high frequencies rostral and with low frequency arranged caudally (Merzenich & Brugge, 1973).

Shortly after neurulation is complete in early embryonic life, the dorsolateral walls of the cerebral vesicles start to form the layers of the cortex by the third week of fetal development. At about the 12th week GA neurons migrate out of the epithelium to form the cortical plate. At this same time, the first stages of the development of the sylvian fissure are recognized (Cant, 1998; Streeter, 1912). The six distinct cortical layers within the cerebral cortex are identified by the 14th week GA (Krmpotic-Nemanic, Kostovic, Nemanic, & Kelovic, 1979; also Bayer, et al., 1995, who estimates neurogenesis is complete in the 16th week GA), and are differentiated by the 24th week GA (Cant, 1998; Streeter, 1912). By the 18th week GA synaptic vesicles are present above and below the cortical plate (Molliver, Kostovic, & van der Loss, 1973), and synaptic terminals with vesicles are present by the 23rd week GA (Krmpotic-Nemanic et al., 1979). By the 27th week GA development of the temporal lobe has begun and just 10 weeks later by the 37th week GA the transverse temporal gyrus and superior temporal gyrus has become apparent (Moore & Guan, 2001).

Axons in cortical layer I mature from the 28th week GA to the fourth postnatal month. Subsequently, axons begin to radiate into the deeper cortical layers--IV, V and VI--of the cortex up to one year of age. By two years of age the laminar organization of the cortex is adult-like and maturation continues in the deep cortical layers until age five. At six years of age mature axons begin to appear in the superficial cortical layers--II and III--and their density is equivalent to that of young adults by 12 years of age (Moore & Guan, 2001; Moore, 2002). Myelination of the associated auditory areas in the cortex matches the protracted cycle of myelination in the reticular formation (Yakovlev & Lecours, 1967).

In summary, the CAP is a collection of nuclei, interconnecting fiber tracts, relay and processing centers that analyze and transmits auditory signals from the ear to the primary

auditory cortex. To relate in brief, the functional bases of the CAP begins with at CN which receives, transforms and relays auditory information to the SOC. The SOC then receives and integrates this information arising from both the ipsilateral and contralateral CN. The LL then carries both afferent and efferent auditory information to the IC. The IC then serves as an obligatory relay center for all auditory fibers. The MGB then sends auditory attention information and multimodal arousal information to the auditory cortex, where it is then processed. In addition, the tonotopic organization established in the cochlea is preserved at all of these levels of the auditory system.

The nuclei of the CAP develop concurrently and are established and functional early in embryonic life, well before cochlear function is demonstrated (Rubel, 1978). From about the third to the eighth week GA, the generation of nuclei across the CAP appears to develop as a unit, with the exception of the IC and the auditory cortex, which continues until about the 17th week GA. The myelination of neurons across the CAP also appears to develop as a unit, from about the 26th week GA until about one year postnatal age, with the exception of the MGB, the reticular formation and the auditory cortex; the MGB demonstrates a condensed cycle whereas the reticular formation and the auditory cortex demonstrate a protracted cycle of myelination (cf. Table 2).

Chapter subsections 3.2 and 3.3 offered a complete overview on the development of the auditory system from the ME to the auditory cortex. The complexities of these systems as they mature differentially affect AEP response characteristics. Subsection 3.4 will detail these changes as transient and steady-state AEPs develop.

Table 2 Embryonic Development of the Central Auditory System

GA	CN	SOC	LL	IC	MGB	ARAS	AI
3rd							Layers of the cortex start formation.
4th			Interstitial nuclei originate until the 7th week			Neurons of the ARAS generate until the 7th week.	
6th				Neurons of the IC generate until the 17th week	Neurons of the MGB develop. Late in the week, the MGB is displaced and begins to migrate until the 8th week.		
7th	Neurons form the CN.		Neurons of the LL generate.				
8th	Differentiation of first and second-order neurons occurs.	Nuclei of the SOC are apparent.					
12th							Cortical plate forms. First stages of the sylvian fissure are recognized.
14th							Six distinct cortical layers are identified.
16th	Cochlear nerve fibers innervate the CN of the brainstem.						
18th							Synaptic vesicles are present above and below the cortical plate.
21st					Cell differentiation begins.		

Table 2 continued.

23rd							Synaptic terminals with vesicles are present above and below the cortical plate.
24th							Cortical layers are differentiated.
26th	Myelin is visualized.	Myelin is visualized.	Myelin is visualized.	Myelin is visualized.			
28th					Myelination begins and is complete by the fourth postnatal month.		Axons in cortical layer I start to mature until the fourth postnatal month. Axons begin to radiate into layers IV, V and VI up to one year of age, and continue to mature until age five.
29th	Myelin increases until term; approximates an adult one year postnatal age	Myelin increases until term; approximates an adult one year postnatal age.	Myelin increases until term; approximates an adult one year postnatal age	Myelin increases until term; approximates an adult one year postnatal age			
30th	Morphology is similar to that of an adult. Additional growth occurs before the 7th postnatal week.						
40th					The MGB is seen in its final shape and location.	Myelination begins one year postnatal age and extends until puberty.	Axons continue to mature in the remaining cortical layers until 12 years of age. Myelination begins one year postnatal age and extends until puberty.

Note: Abbreviations as used in Table 1.

3.4 DEVELOPMENT OF AUDITORY EVOKED POTENTIALS

Because response amplitude and latency (or phase) changes seen in various electrophysiological tests reflect the growth of the auditory system--particularly increased myelination, synaptic density and efficacy--chapter subsections will detail age-related changes (i.e., preterm to adult) as each AEP, evoked by transient and steady-state stimuli, undergoes development. Although, the preterm and term data contained in this section does not contribute specifically to the hypotheses or methods of this dissertation study, the review of this literature provides a broad framework within which the development and maturity of AEPs is contingent upon.

3.4.1 Evoked by transient stimuli

3.4.1.1 ABR

The infant ABR is incomplete at birth and differs from an adult in virtually all measurement parameters. Reliable components of the ABR have been successfully recorded in preterm infants as early as the 27th week GA (Rotteveel, de Graff et al., 1987a; Starr et al., 1977) (cf. Tables 3-9 and Figures 2-4). The infant ABR is typically characterized as a series of three primary vertex-positive peaks (I, III and V); wave I being the most prominent followed by wave V (Stockard & Stockard, 1980; Stockard & Stockard, 1983). Age-related changes, in absolute and interpeak measurements, with development have been attributed to maturational changes in nerve conduction velocity and synaptic efficacy along the neonatal auditory nerve and brainstem. Although the waveform morphology of an infant response is markedly different from those of an adult, the infant response reaches adult configuration between three and six months of age

(Salamy & McKean, 1976). However, since preterm birth slightly delays early maturation of the more central regions of the brainstem, the ABR components reach term values in these infants at a slightly later term age (Jiang, Brosi, Wu, & Wilkinson, 2009).

Table 3 Mean Latency Values of ABR Wave I in Preterm Infants

Wave I Latencies								
Study	**27-29**	**30-31**	**32-33**	**34-35**	**36-37**	**38-39**	**40-43**	**37-42 GA**
Amin, Orlando, Dalzell, Merle, & Guillet (1999) [a]	3.11 (0.70)	2.54 (0.52)						
Despland & Galambos (1982)		3.50 (0.53)	2.78 (0.22)	2.56 (0.25)	2.53 (0.19)	2.30 (0.19)	2.28 (0.27)	
Eggermont & Salamy (1988)				2.57 (0.54)		2.41 (0.38)	2.00 (0.31)	
Eldredge & Salamy (1996)								1.45 (0.27)
Fawer & Dubowitz (1982)		3.58 (0.32)	3.27 (0.31)	2.99 (0.30)	2.77 (0.32)	2.57 (0.31)	2.42 (0.32)	
Goldstein et al. (1979)		2.75 (0.68)	2.02 (0.39)	1.87 (0.23)	1.71 (0.18)			1.64 (0.18)
Jiang, Brosi, Wang, & Wilkinson (2004) [b]			2.36 (0.21)					2.28 (0.18)
Jiang, Brosi, & Wilkinson (1998)								2.33 (0.17)
Jiang, Brosi, & Wilkinson (2002) [c]	2.42 (0.16)							2.33 (0.21)
Jiang & Wilkinson (2008)								2.29 (0.18)
Krumholz et al. (1985)			2.76 (0.56)	2.29 (0.51)	2.25 (0.52)	2.19 (0.46)	1.86 (0.18)	
Lasky (1984)				3.30 (0.50)		3.10 (0.40)	3.00 (0.60)	
Lina-Granade, Collet, Morgan & Salle (1993)				2.68 (0.79)	2.13 (0.31)	2.40 (0.19)	2.13 (0.58)	
Mochizuki et al. (1982)					1.62 (0.13)			1.58 (0.15)
Rotteveel, de Graaf et al. (1987a)	4.33 (0.49)	4.16 (0.69)	3.61 (0.63)	3.25 (0.60)	3.15 (0.65)	3.00 (0.54)	2.74 (0.38)	
Salamy et al. (1982)			2.90 (0.70)	2.55 (0.47)		2.43 (1.40)	2.07 (0.36)	

Table 3 continued.

Starr et al. (1977) [e]		3.20	2.90	2.60	2.00	1.90	1.80	
Stockard et al. (1978)				2.70	2.30			
Stockard et al. (1983)						1.88 (0.20)	1.81 (0.22)	
Stockard & Westmoreland (1981)						1.80 (0.12)	1.81 (0.22)	

Note: Comparative survey of mean latency values of ABR waves in preterm infants. Mean latency values are in msec; SDs (in parentheses). Click stimuli were used in all the above studies. Click rate ranged from 10 to 39.9 per sec. GA=gestational age. Discrepancies across studies may be due to variations in equipment, methods and recording conditions. Data are displayed in Figures 2, 3 and 4. In some studies latency and amplitude values for preterm infants 37-42 and 40-43 GA were grouped together. These values are denoted in the last column of all preterm tables; however, they are not represented in the corresponding Figures. Abbreviations and footnotes also used in Tables 4-9.

[a] Mean latency values published for 'Day 5'.

[b] Mean latency values published for the mean GA 33.6 weeks.

[c] Mean latency values published for the mean GA 28 weeks.

[d] Mean latency values also published in Salamy (1984).

[e] Mean latency values published in Starr & Amlie (1981).

[f] Mean latency values of the ABR Wave V in preterm infants for the right ear.

[g] Mean latency values of the ABR Wave V in preterm infants for the left ear.

Table 4 Mean Latency Values of ABR Wave III in Preterm Infants

Wave III Latencies								
Study	**27-29**	**30-31**	**32-33**	**34-35**	**36-37**	**38-39**	**40-43**	**37-42 GA**
Amin et al. (1999) [a]	6.21 (0.82)	5.70 (0.55)						
Eggermont & Salamy (1988)				5.68 (0.75)		5.35 (0.49)	4.82 (0.44)	
Eldredge & Salamy (1996)								4.14 (0.34)
Goldstein et al. (1979)		6.40 (0.89)	4.97 (0.54)	4.77 (0.31)	4.52 (0.18)			4.43 (0.24)
Jiang et al. (2004) [b]			5.10 (0.23)					5.04 (0.19)
Jiang et al. (1998)								5.12 (0.25)
Jiang et al. (2002) [c]	5.10 (0.26)							5.08 (0.24)
Jiang & Wilkinson (2008)								5.04 (0.19)
Krumholz et al. (1985)			5.84 (0.95)	5.40 (0.64)	5.11 (0.62)	5.09 (0.49)	4.62 (0.26)	
Lasky (1984)				5.70 (0.70)		5.30 (0.30)	5.40 (0.50)	
Lina-Granade et al. (1993)				4.76 (0.48)	4.66 (0.38)	4.52 (0.27)	4.53 (0.32)	
Mochizuki et al. (1988)					4.57 (0.27)			4.35 (0.19)
Rotteveel, de Graaf et al. (1987a)	7.80	7.39 (0.67)	6.94 (0.77)	6.35 (0.79)	6.14 (0.81)	5.79 (0.56)	5.56 (0.57)	
Salamy et al. (1982) [d]			5.97 (1.12)	5.73 (0.55)		5.32 (0.44)	4.84 (0.46)	
Stockard & Westmoreland (1981)						4.80 (0.16)	4.62 (0.29)	

Table 5 Mean Latency Values of ABR Wave V in Preterm Infants

Wave V Latencies								
Study	**27-29**	**30-31**	**32-33**	**34-35**	**36-37**	**38-39**	**40-43**	**37-42 GA**
Amin et al. (1999) [a]	9.66 (1.14)	8.66 (0.71)						
Despland & Galambos (1982)		9.10 (0.32)	8.36 (0.54)	8.00 (0.28)	7.80 (0.45)	7.42 (0.19)	7.35 (0.46)	
Eggermont & Salamy (1988)				8.21 (0.79)		7.83 (0.59)	7.14 (0.43)	
Eldredge & Salamy (1996)								6.40 (0.33)
Fawer & Dubowitz (1982)		9.06 (0.36)	8.50 (0.37)	8.03 (0.36)	7.67 (0.38)	7.43 (0.37)	7.29 (0.37)	
Goldstein et al. (1979)		8.77 (0.38)	7.62 (0.47)	7.52 (0.42)	7.33 (0.48)			6.74 (0.22)
Jiang et al. (2004) [b]			7.29 (0.24)					7.19 (0.20)
Jiang et al. (1998)								7.24 (0.23)
Jiang et al. (2002) [c]	7.40 (0.33)							7.22 (0.23)
Jiang & Wilkinson (2008)								7.20 (0.20)
Krumholz et al. (1985)			8.94 (1.30)	7.81 (0.78)	7.46 (0.46)	7.24 (0.41)	6.80 (0.28)	
Lasky (1984)				8.70 (0.60)		8.10 (0.50)	7.60 (0.50)	
Lina-Granade et al. (1993)				7.53 (0.62)	7.19 (0.48)	6.94 (0.33)	6.96 (0.45)	
Mochizuki et al. (1988)					7.04 (0.29)			6.76 (0.25)
Rotteveel, de Graaf et al. (1987a)	11.50 (0.78)	10.70 (0.86)	9.45 (0.89)	8.76 (0.85)	8.40 (0.75)	8.05 (0.52)	7.65 (0.42)	
Salamy et al. (1982) [d]			7.91 (1.22)	8.22 (0.54)		7.84 (0.49)	7.16 (0.44)	

Table 5 continued.

Starr et al. (1977) [e]		9.00	8.20	7.60	7.30	7.00	6.90	
Stockard et al. (1978)				8.50	7.40			
Stockard et al. (1983)						7.17 (0.27)	6.72 (0.32)	
Stockard & Westmoreland (1981)						7.07 (0.27)	6.72 (0.32)	
Vles, Casaer, Kingma, Swennen, & Daniels (1987) [f]			7.90 (0.40)					
Vles et al. (1987) [g]			8.00 (0.30)					

Table 6 Mean Interpeak Latency Values of ABR Wave I-III in Preterm Infants

Wave I-III								
Study	**27-29**	**30-31**	**32-33**	**34-35**	**36-37**	**38-39**	**40-43**	**37-42 GA**
Amin et al. (1999) [a]	3.22 (0.72)	3.01 (0.60)						
Eggermont & Salamy (1988)				3.13 (0.56)		2.93 (0.45)	2.80 (0.38)	
Eldredge & Salamy (1996)								2.69 (0.24)
Goldstein et al. (1979)		3.13 (0.37)	2.85 (0.30)	2.90 (0..38)	2.81 (0.24)			
Jiang et al. (2004) [b]			2.74 (0.22)					2.77 (0.15)
Jiang et al. (1998)								2.78 (0.18)
Jiang et al. (2002) [c]	2.67 (0.24)							2.74 (0.17)
Jiang & Wilkinson (2008)								2.75 (0.15)
Krumholz et al. (1985)			3.07 (0.97)	2.95 (0.34)	2.93 (0.42)	2.75 (0.27)	2.76 (0.27)	
Lina-Granade et al. (1993)				2.70 (0.43)	2.71 (0.31)	2.48 (0.23)	2.57 (0.15)	
Rotteveel, de Graaf et al. (1987a)	3.20	3.49 (0.49)	3.30 (0.46)	3.07 (0.34)	2.99 (0.50)	2.78 (0.32)	2.82 (0.40)	
Salamy (1982)			3.14 (1.31)	3.21 (0.45)		2.89 (0.33)	2.78 (0.36)	
Stockard & Westmoreland (1981)						2.99 (0.19)	2.78 (0.21)	

Table 7 Mean Interpeak Latency Values of ABR Wave III-V in Preterm Infants

Wave III-V								
Study	**27-29**	**30-31**	**32-33**	**34-35**	**36-37**	**38-39**	**40-43**	**37-42 GA**
Amin et al. (1999) [a]	3.16 (0.85)	2.88 (0.43)						
Eggermont & Salamy (1988)				2.53 (0.48)		2.47 (0.46)	2.31 (0.44)	
Eldredge & Salamy (1996)								2.26 (0.25)
Goldstein et al. (1979)		2.63 (0.54)	2.49 (0.38)	2.53 (0..39)	2.60 (0.44)			
Jiang et al. (2004) [b]			2.20 (0.14)					2.18 (0.11)
Jiang et al. (1998)								2.17 (0.11)
Jiang et al. (2002) [c]	2.29 (0.19)							2.16 (0.11)
Jiang & Wilkinson (2008)								2.18 (0.11)
Krumholz et al. (1985)			2.97 (0.93)	2.61 (0.37)	2.50 (0.31)	2.28 (0.25)	2.18 (0.27)	
Lina-Granade et al. (1993)				2.69 (0.24)	2.56 (0.27)	2.42 (0.23)	2.35 (0.29)	
Rotteveel, de Graaf et al. (1987a)	3.20	3.12 (0.50)	2.57 (0.45)	2.41 (0.44)	2.29 (0.44)	2.23 (0.24)	2.09 (0.40)	
Salamy (1982)			2.10 (0.37)	2.51 (0.46)		2.49 (0.46)	2.30 (0.39)	
Stockard & Westmoreland (1981)						2.27 (0.29)	2.15 (0.23)	

Table 8 Mean Interpeak Latency Values of ABR Wave I-V in Preterm Infants

Wave I-V								
Study	**27-29**	**30-31**	**32-33**	**34-35**	**36-37**	**38-39**	**40-43**	**37-42 GA**
Amin et al. (1999) [a]	6.86 (0.69)	5.88 (0.67)						
Despland & Galambos (1982)		5.60 (0.55)	5.62 (0.30)	5.44 (0.29)	5.27 (0.38)	5.09 (0.16)	5.07 (0.41)	
Eggermont & Salamy (1988)				5.64 (0.70)		5.43 (0.55)	5.14 (0.40)	
Eldredge & Salamy (1996)								4.95 (0.24)
Fawer & Dubowitz (1982)		5.49 (0.27)	5.23 (0.27)	5.03 (0.26)	4.90 (0.26)	4.85 (0.26)	4.87 (0.27)	
Goldstein et al. (1979)		5.76 (0.78)	5.34 (0.53)	5.42 (0.54)	5.41 (0.59)			
Jiang et al. (2004) [b]			4.94 (0.22)					4.96 (0.17)
Jiang et al. (1998)								4.96 (0.20)
Jiang et al. (2002) [c]	4.97 (0.27)							4.90 (0.17)
Jiang & Wilkinson (2008)								4.93 (0.20)
Krumholz et al. (1985)		7.69 (1.23)	6.05 (0.93)	5.60 (0.35)	5.36 (0.48)	5.10 (0.42)	4.92 (0.29)	
Lina-Granade et al. (1993)				5.36 (0.45)	5.26 (0.42)	4.78 (0.40)	4.81 (0.58)	
Mochizuki et al. (1988)					5.42 (0.33)			5.18 (0.26)
Rotteveel, Colon et al. (1987a)		6.30 (0.60)	5.60 (0.20)	5.30 (0.20)	5.10 (0.20)	5.00 (0.20)	4.80 (0.10)	
Rotteveel, de Graaf et al. (1987a)	7.07 (1.19)	6.52 (0.30)	5.83 (0.47)	5.50 (0.48)	5.29 (0.42)	5.01 (0.31)	4.91 (0.31)	
Salamy et al. (1982) [d]			5.16 (1.48)	5.67 (0.54)		5.41 (0.14)	5.09 (0.42)	

Table 8 continued.

Starr et al. (1977) [e]		6.40	5.40	5.30	5.30	5.10	5.00	
Stockard et al. (1983)						5.26 (0.31)	4.90 (0.28)	
Stockard & Westmoreland (1981)						5.27 (0.31)	4.90 (0.27)	
Vles et al (1987) [f]			5.70 (0.40)					
Vles et al. (1987) [g]			5.80 (0.30)					

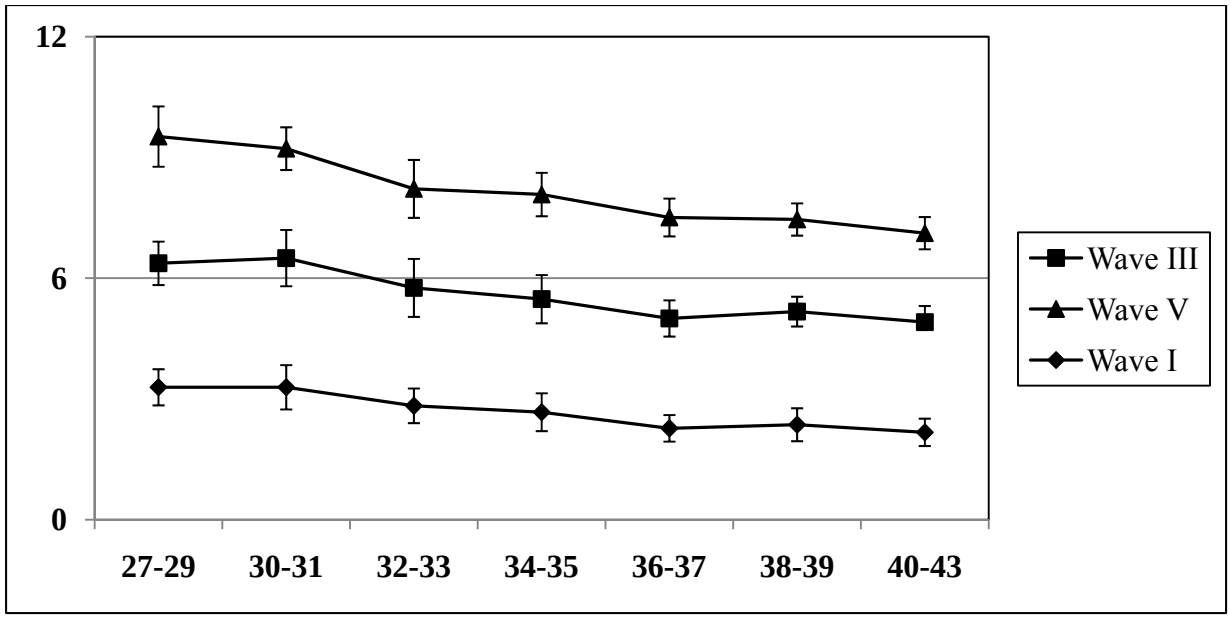


Figure 2 Summary of Latency Values of ABR Waves in Preterm Infants

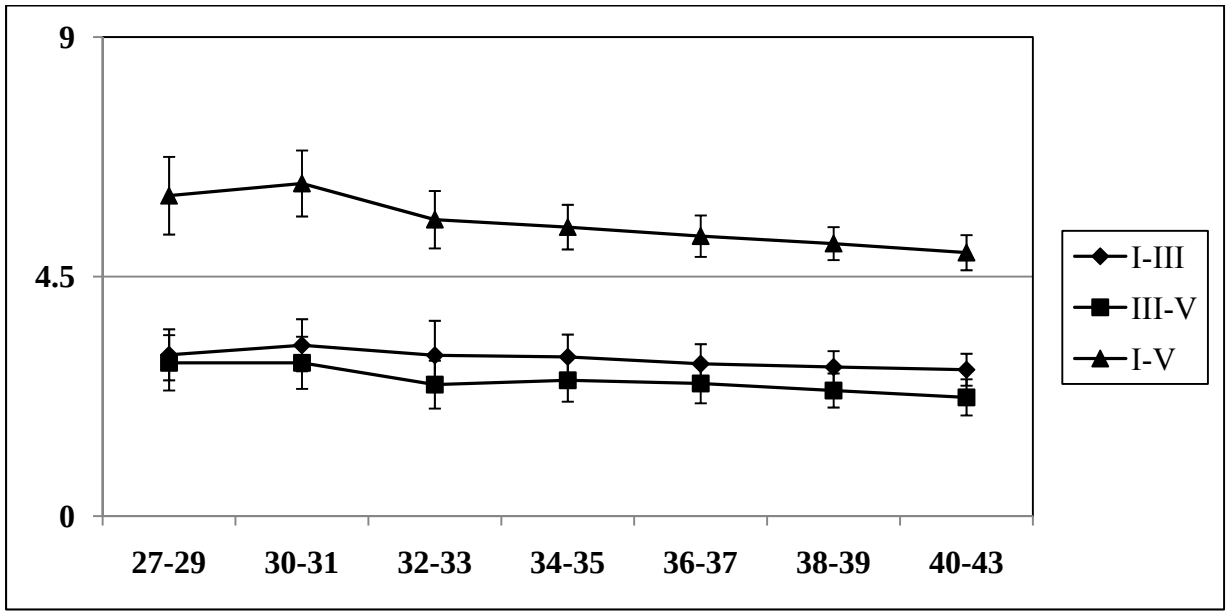


Figure 3 Summary of Interpeak Latency Values of ABR Waves in Preterm Infants

Table 9 Mean Amplitude and Ratio Values of ABR Waves in Preterm Infants

Study	27-29	30-31	32-33	34-35	36-37	38-39	40-43 GA
Wave I Amplitudes							
Jiang et al. (2004) [b]			0.18 (0.05)				
Jiang et al. (2002) [c]	0.17 (0.06)						
Lasky (1984)			0.11 (0.04)		0.13 (0.06)		0.20 (0.10)
Rotteveel, de Graaf et al. (1987a)	0.07 (0.04)	0.14 (0.07)	0.14 (0.10)	0.16 (0.06)	0.16 (0.07)	0.17 (0.07)	0.18 (0.07)
Salamy et al. (1982) [d]			0.08 (0.03)	0.13 (0.06)		0.14 (0.05)	0.15 (0.60)
Wave III Amplitudes							
Jiang et al. (2004) [b]			0.26 (0.05)				
Jiang et al. (2002) [c]	0.24 (0.08)						
Lasky (1984)			0.15 (0.05)		0.17 (0.05)		0.25 (0.08)
Rotteveel, de Graaf et al. (1987a)	-0.01	0.08 (0.05)	0.06 (0.07)	0.07 (0.06)	0.08 (0.06)	0.08 (0.05)	0.09 (0.06)
Salamy et al. (1982) [d]			0.05 (0.02)	0.10 (0.05)		0.09 (0.05)	0.09 (0.04)
Wave V Amplitudes							
Jiang et al. (2004) [b]			0.22 (0.05)				
Jiang et al. (2002) [c]	0.20 (0.06)						
Lasky (1984)			0.14 (0.06)		0.15 (0.06)		0.28 (0.13)
Rotteveel, de Graaf et al. (1987a)	0.05 (0.06)	0.08 (0.04)	0.09 (0.05)	0.12 (0.07)	0.13 (0.05)	0.16 (0.06)	0.19 (0.07)
Salamy et al. (1982) [d]			0.11 (0.04)	0.12 (0.05)		0.17 (0.07)	0.17 (0.06)

Table 9 continued.

V-I Interpeak Ratio							
Jiang et al. (2004) [b]			1.42 (0.51)				
Jiang et al. (2002) [c]	1.45 (0.12)						
Krumholz et al. (1985)		1.05 (0.66)	1.36 (0.59)	1.20 (0.62)	1.34 (0.73)	1.50 (0.55)	1.89 (0.82)
Rotteveel, Colon et al. (1987a)		0.22 (0.07)	0.36 (0.09)	0.61 (0.15)	0.63 (0.24)	0.94 (0.29)	0.94 (0.32)
Rotteveel, de Graaf et al. (1987a)			0.70 (1.30)	0.80 (0.50)	0.90 (0.60)	1.10 (0.60)	1.10 (0.50)
Salamy et al. (1982) [d]			1.46 (0.62)	1.10 (0.80)		1.32 (0.59)	1.33 (0.86)

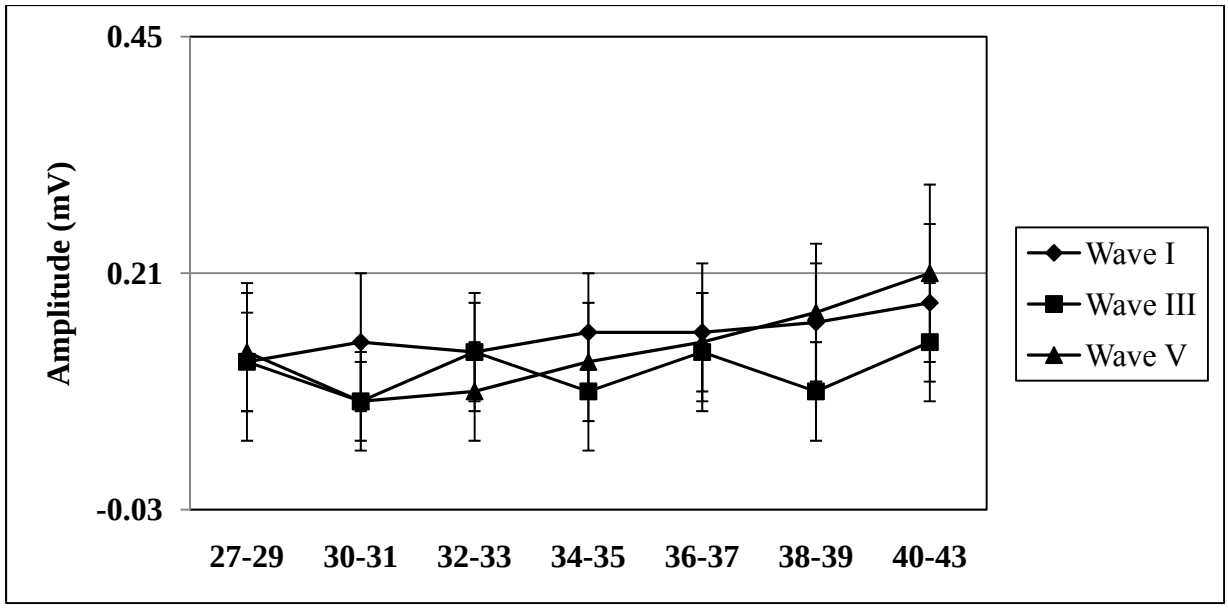


Figure 4 Summary of Amplitude Values of ABR Waves in Preterm Infants

The majority of investigators agree that prior to the third month of life, absolute latency values for wave I do not alter significantly with increasing age, thereby suggesting that middle ear and auditory nerve transmission is very close to maturity in a term birth (Beiser, Himelfarb, Gold, & Shanon, 1985; Eggermont & Salamy, 1988; Fria & Doyle, 1984; Gafni, Sohmer, Gross, Weizman, & Robinson, 1980; Goldstein, Krumholz, Felix, Shannon, & Carr, 1979; Gorga, Kaminski, Beauchaine, Jesteadt, & Neely, 1989; Hecox & Burkard, 1982; Hurley, Hurley, & Berlin, 2005; Inagaki et al., 1987; Jiang, Zheng, Sun, & Liu, 1991; Krumholz, Felix, Goldstein, & McKenzie, 1985; Mochizuki, Go, Ohkubo, Tatara, & Motomura, 1982; Morgan, Zimmerman, & Dubno, 1987; Paludetti, Maurizi, Ottaviani, & Rosignoli, 1981; Salamy 1984; Salamy, McKean, & Buda, 1975; Salamy & McKean, 1976; Salamy, McKean, Pettett, & Mendelson, 1978; Salamy, Mendelson, & Tooley, 1982; Salamy, Mendelson, Tooley, & Chaplin, 1980;

Stockard et al., 1979; Zimmerman, Morgan, & Dubno, 1987). Absolute latency changes for waves III and V are much more pronounced than for wave I and continue to decrease post-term (Beiser et al., 1985; Goldstein et al., 1979; Hurley et al., 2005; Krumholz et al., 1985; Paludetti et al., 1981; Salamy & McKean, 1976; Salamy et al., 1982; Salamy et al., 1980; Schwartz, Pratt, & Schwartz, 1989; Zimmerman et al., 1987), until about the second year of life (Eggermont & Salamy, 1988; Fria & Doyle, 1984; Gorga et al., 1989; Hecox & Burkard, 1982; Hecox & Galambos, 1974; Inagaki et al., 1987; Jiang et al., 1991; Mochizuki et al., 1982; Salamy 1984; Salamy et al., 1975) (cf. Tables 10, 11, 12 and Figure 5), demonstrating a caudal-to-rostral, or peripheral-to-central, progression of auditory neurodevelopment.

Table 10 Mean Latency Values of ABR Wave I in Term Infants to Adulthood

Wave I						
Study	**Term**	**3M**	**18M-2Y**	**3Y**	**5Y**	**Adult**
Beiser et al. (1985)	1.55 (0.13)	1.52 (0.14)	1.46 (0.09)			1.38 (0.06)
Chiappa et al. (1979)						1.70 (0.15)
Despland & Galambos (1980) [a]	2.28 (0.27)					
Eggermont & Salamy (1988)	2.00 (0.31)	1.69 (0.22)	1.66 (0.12)	1.66 (0.11)	1.66 (0.09)	1.70 (0.16)
Eldredge & Salamy (1996)	1.45 (0.27)					
Fawer & Dubowitz (1982)	2.42 (0.32)					
Gafni et al. (1980)	1.65 (0.19)	1.56 (0.21)				
Goldstein et al. (1979)	1.64 (0.18)					1.53 (0.14)
Gorga et al. (1989)		1.60 (0.17)	1.57 (0.17)	1.56 (0.15)		
Jiang et al. (2004)	2.28 (0.18)					
Jiang et al. (1998)	2.33 (0.17)					2.13 (0.12)
Jiang et al. (2002)	2.33 (0.21)					
Jiang & Wilkinson (2008)	2.29 (0.18)					
Jiang et al. (1991)	1.94 (0.17)	1.90 (0.16)	1.80 (0.18)	1.76 (0.15)	1.70 (0.20)	1.71 (0.11)
Krumholz et al. (1985)	1.86 (0.18)					1.68 (0.12)
Lasky (1984)	3.00 (0.60)					1.60 (0.30)

Table 10 continued.

Lima, Alvarenga, Foelkel, Monteiro & Agostinho (2008)						1.68 (0.12)
Lina-Granade et al. (1993)	2.13 (0.58)					1.72 (0.11)
Mochizuki et al. (1982) [c]	1.58 (0.15)	1.49 (0.12)	1.51 (0.11)	1.51 (0.11)	1.42 (0.08)	1.37 (0.06)
Morgan et al. (1987) [d]	2.03 (0.39)					1.71 (0.14)
Pasman, Rotteveel, de Graff, Maassen, & Visco (1996)	2.56 (0.41)					
Pasman, Rotteveel, de Graff, Stegeman, & Visco (1992)	2.56 (0.50)	2.15 (0.37)				
Rotteveel, Colon et al. (1986a)	2.58 (0.48)	2.14 (0.37)				
Rotteveel, de Graff et al. (1987a)	2.74 (0.38)	2.31 (0.39)				
Salamy & McKean (1976) [e]	2.12 (0.35)	1.82 (0.27)				1.57 (0.14)
Salamy et al. (1978)	2.12 (0.36)	1.71 (0.38)		1.68 (0.20)		1.51 (0.08)
Salamy et al. (1978)	2.17 (0.32)	1.71 (0.36)		1.79 (0.46)		1.55 (0.12)
Salamy et al. (1982) [f]	2.07 (0.36)	1.70 (0.27)			1.70 (0.16)	1.29 (0.15)
Scherg & Speulda (1982)						1.82 (0.16)
Sohmer et al. (1978)					1.34 (0.11)	
Starr et al. (1977) [g]	1.80					1.60
Stockard et al (1983)	1.81 (0.22)					
Stockard et al. (1979)	1.81 (0.22)					1.62 (0.12)

Table 10 continued.

Stockard & Westmoreland (1981)	1.81 (0.22)					
Zimmerman et al. (1987)	2.05 (0.35)	1.73 (0.16)				1.71 (0.14)

Note: Comparative survey of mean latency values of ABR waves in term infants to adulthood. Mean latency values are in msec; SDs (in parentheses). Click stimuli were used in all the above studies. Click rate ranged from 10 to 23 per sec. M=month. Y= year. Term is defined as 37-43 weeks GA. Adults were typically defined by investigators as > 15 years of age. In some studies latency and SD values for children and adults were grouped together (ranging from 5-33 years of age). In these cases ([c], [d], and [e]), mean latency and SD values were defined in the Table above as adult. Discrepancies across studies may be due to variations in equipment, methods and recording conditions. Data are displayed in Figure 5. Age ranges displayed were based on infant responses reaching adult value by two years of age. Abbreviations and footnotes also used in Tables 11 and 12.

[a] Means and SDs of latency values published in Rotteveel, Colon et al. (1986a), and also published by Despland & Galambos (1982).

[b] Estimated adult response latency value from Figure 4 in Despland & Galambos (1980).

[f] Mean latency values also published in Salamy (1984).

[g] Mean latency values published in Starr & Amlie (1981).

Table 11 Mean Latency Values of ABR Wave III in Term Infants to Adulthood

Wave III						
Study	**Term**	**3M**	**18M-2Y**	**3Y**	**5Y**	**Adult**
Beiser et al. (1985)	4.45 (0.23)	4.41 (0.21)	3.78 (0.09)			3.61 (0.15)
Chiappa et al. (1979)						3.90 (0.19)
Eggermont & Salamy (1988)	4.82 (0.44)	4.12 (0.34)	3.84 (0.16)	3.81 (0.15)	3.85 (0.17)	3.72 (0.15)
Eldredge & Salamy (1996)	4.14 (0.34)					
Goldstein et al. (1979)	4.43 (0.24)					3.63 (0.18)
Jiang et al. (2004)	5.04 (0.19)					
Jiang et al. (1998)	5.12 (0.25)					4.28 (0.15)
Jiang et al. (2002)	5.08 (0.24)					
Jiang & Wilkinson (2008)	5.04 (0.19)					
Jiang et al. (1991)	4.78 (0.23)	4.67 (0.19)	4.21 (0.28)	3.99 (0.19)	3.92 (0.17)	3.80 (0.15)
Krumholz et al. (1985)	4.62 (0.26)					3.78 (0.19)
Lasky (1984)	5.40 (0.50)					3.90 (0.40)
Lima et al. (2008)						3.75 (0.21)
Lina-Granade et al. (1993)	4.53 (0.32)					3.88 (0.14)
McPherson et al. (1989)	4.90 (0.30)					4.30 (0.40)
Mochizuki et al. (1982) [c]	4.35 (0.19)	4.12 (0.14)	3.80 (0.17)	3.81 (0.13)	3.62 (0.14)	3.59 (0.14)

Table 11 continued.

Morgan et al. (1987) [d]	4.74 (0.42)					3.80 (0.17)
Pasman et al. (1996)	5.47 (0.49)					
Pasman et al. (1992)	5.43 (0.54)	4.62 (0.41)				
Rotteveel, Colon et al. (1986a)	5.45 (0.55)	4.62 (0.41)				
Rotteveel, de Graff et al. (1987a)	5.56 (0.57)	4.88 (0.48)				
Salamy & McKean (1976) [e]	4.89 (0.35)	4.15 (0.20)				3.64 (0.24)
Salamy et al. (1978)	4.91 (0.36)	4.25 (0.36)		3.99 (0.44)		3.67 (0.10)
Salamy et al. (1978)	4.99 (0.32)	4.38 (0.39)		4.00 (0.48)		3.66 (0.11)
Salamy et al. (1982) [f]	4.84 (0.46)	4.23 (0.25)			3.80 (0.21)	3.72 (0.15)
Scherg & Speulda (1982)						3.97 (0.17)
Sohmer et al. (1978)					3.51 (0.14)	
Stockard et al. (1978)						3.95
Stockard et al. (1979)	4.62 (0.29)					3.75 (0.17)
Stockard & Westmoreland (1981)	4.62 (0.29)					
Zimmerman et al. (1987)	4.75 (0.43)	4.28 (0.25)				3.80 (0.17)

Table 12 Mean Latency Values of ABR Wave V in Term Infants to Adulthood

Wave V						
Study	**Term**	**3M**	**18M-2Y**	**3Y**	**5Y**	**Adult**
Beiser et al. (1985)	6.67 (0.29)	6.46 (0.28)	5.74 (0.22)			5.54 (0.15)
Chiappa et al. (1979)						5.70 (0.25)
Despland & Galambos (1980) [a, b]	7.35 (0.46)					5.60
Eggermont & Salamy (1988)	7.14 (0.43)	6.40 (0.22)	5.86 (0.19)	5.81 (0.32)	5.68 (0.21)	5.66 (0.23)
Eldredge & Salamy (1996)	6.40 (0.33)					
Fawer & Dubowitz (1982)	7.29 (0.37)					
Goldstein et al. (1979)	6.74 (0.22)					5.56 (0.20)
Gorga et al. (1989)		6.25 (0.32)	5.71 (0.26)	5.68 (0.27)		
Jiang et al. (2004)	7.19 (0.20)					
Jiang et al. (1998)	7.24 (0.23)					6.14 (0.13)
Jiang et al. (2002)	7.22 (0.23)					
Jiang & Wilkinson (2008)	7.20 (0.20)					
Jiang et al. (1991)	6.84 (0.23)	6.66 (0.21)	6.01 (0.29)	5.81 (0.20)	5.69 (0.19)	5.64 (0.18)
Krumholz et al. (1985)	6.80 (0.28)					5.67 (0.21)
Lasky (1984)	7.60 (0.50)					5.70 (0.40)
Lima et al. (2008)						5.56 (0.26)

Table 12 continued.

Lina-Granade et al. (1993)	6.96 (0.45)					5.70 (0.18)
McPherson et al. (1989)	7.50 (0.40)					6.10 (0.30)
Mochizuki et al. (1982) [c]	6.76 (0.25)	6.46 (0.23)	5.86 (0.23)	5.83 (0.23)	5.53 (0.19)	5.51 (0.21)
Morgan et al. (1987) [d]	6.91 (0.39)					5.54 (0.22)
Pasman et al. (1996)	7.53 (0.41)					
Pasman et al. (1992)	7.51 (0.43)	6.72 (0.32)				
Rotteveel, Colon et al. (1986a)	7.53 (0.43)	6.72 (0.31)				
Rotteveel, de Graff et al. (1987a)	7.65 (0.42)	7.03 (0.51)				
Salamy & McKean (1976) [e]	7.06 (0.38)	6.40 (0.29)				5.55 (0.26)
Salamy et al. (1978)	7.11 (0.28)	6.44 (0.33)		5.99 (0.64)		5.39 (0.24)
Salamy et al. (1978)	7.32 (0.27)	6.51 (0.36)		5.98 (0.58)		5.27 (0.33)
Salamy et al. (1982) [f]	7.16 (0.44)	6.45 (0.33)			5.71 (0.23)	5.66 (0.23)
Scherg & Speulda (1982)						5.87 (0.23)
Sohmer et al. (1978)					6.20 (2.07)	
Starr et al. (1977) [g]	6.90					5.70
Stockard et al. (1983)	6.72 (0.32)					
Stockard et al. (1978)						5.85

Table 12 continued.

Stockard & Westmoreland (1981)	6.72 (0.32)					
Weber & Fujikawa (1977)						5.84 (0.30)
Zimmerman et al. (1987)	6.87 (0.40)	6.26 (0.25)				5.54 (0.22)

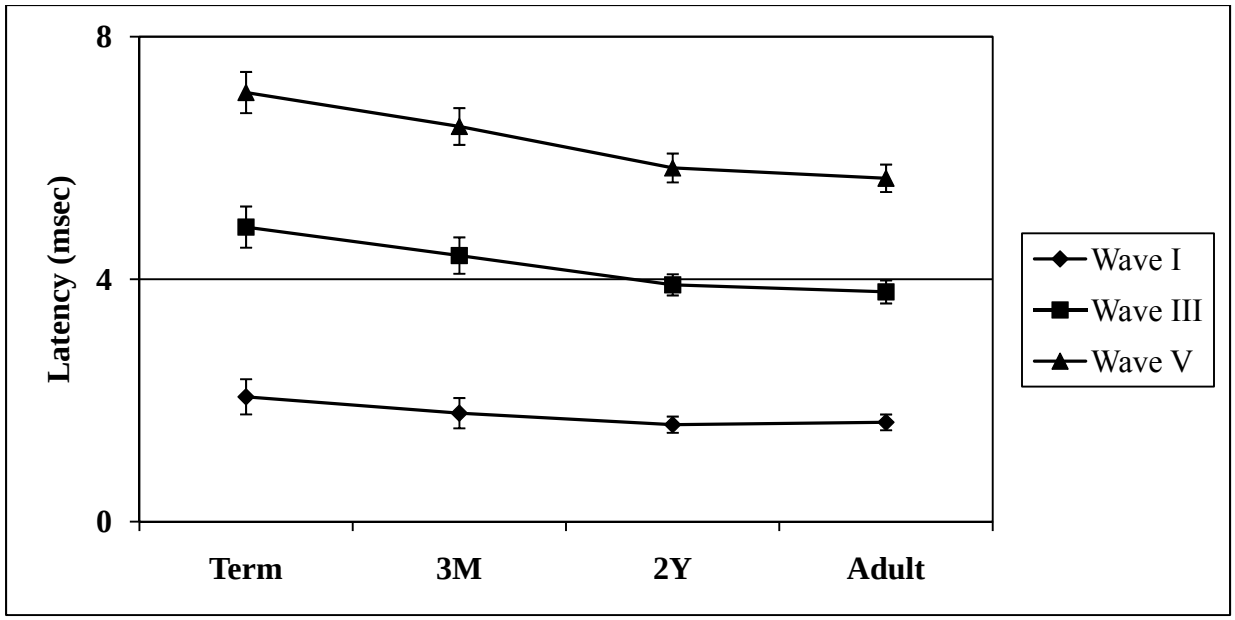


Figure 5 Summary of Latency Values of ABR Waves

Interpeak intervals also show an age dependency, with longer latencies and greater intersubject variability in newborns compared to adults (Hecox & Galambos, 1974; Hecox & Burkard, 1982; Morgan et al., 1987; Rotteveel, de Graff et al., 1987a). Investigators speculate that this age dependency is due to less advanced myelination (which gives rise to lower conduction velocity) along the auditory pathway in newborns (Hecox & Galambos, 1974; Lieberman, Sohmer, & Szabo, 1973; Salamy & McKean, 1976).

There is considerable variability among investigations regarding the developmental time course of interpeak latency values (cf. Tables 13, 14, 15 and Figure 6). Some studies have reported the I-III interval to be slower in maturation than the III-V (Jiang et al., 1991; Hecox & Burkard, 1982). Other investigations have reported the III-V interval to be slower in maturation than the I-III and I-V interval (Salamy, 1984; Schwartz et al., 1989); while still others have reported the III-V did not vary as a function of age (Fria & Doyle, 1984; Zimmerman et al.,

1987). Although a variety of growth trends have been suggested for interpeak latency values, these trends demonstrate differential maturation of the structures along the neurophysiological pathway of the ABR.

Table 13 Mean Interpeak Latency Values of ABR Wave I-III in Term Infants to Adulthood

Wave I-III						
Study	**Term**	**3M**	**18M-2Y**	**3Y**	**5Y**	**Adult**
Beiser et al. (1985)	2.90 (0.19)	2.89 (0.19)	2.32 (0.14)			2.23 (0.10)
Chiappa et al. (1979)						2.10 (0.15)
Eggermont & Salamy (1988)	2.80 (0.38)	2.49 (0.44)	2.19 (0.17)	2.14 (0.16)	2.19 (0.21)	2.13 (0.21)
Eldredge & Salamy (1996)	2.69 (0.24)					
Gorga et al. (1989)		2.52 (0.22)	2.17 (0.21)	2.17 (0.20)		
Jiang et al. (2004)	2.77 (0.15)					
Jiang et al. (1998)	2.78 (0.18)					2.15 (0.16)
Jiang et al. (2002)	2.74 (0.17)					
Jiang & Wilkinson (2008)	2.75 (0.15)					
Jiang et al. (1991)	2.83 (0.18)	2.77 (0.17)	2.38 (0.19)	2.23 (0.15)	2.21 (0.15)	2.09 (0.15)
Krumholz et al. (1985)	2.76 (0.27)					2.11 (0.13)
Lima et al. (2008)						2.06 (0.21)
Lina-Granade et al. (1993)	2.57 (0.15)					2.16 (0.15)
Morgan et al. (1987) [b]	2.71 (0.33)					2.09 (0.15)
Pasman et al. (1996)	2.91 (0.44)					
Pasman et al. (1992)	2.88 (0.38)	2.47 (0.23)				

Table 13 continued.

Rotteveel et al. (1985)	2.80	2.64				
Rotteveel, Colon et al. (1986a)	2.86 (0.40)	2.46 (0.22)				
Rotteveel, de Graaf et al. (1987a)	2.82 (0.40)	2.56 (0.28)				
Salamy et al. (1982)	2.78 (0.36)	2.54 (0.22)		2.11 (0.21)		2.13 (0.22)
Scherg & Speulda (1982)						2.14 (0.16)
Stockard et al. (1978)						2.11
Stockard et al. (1979)	2.80 (0.21)					2.13 (0.15)
Stockard & Westmoreland (1981)	2.78 (0.21)					
Zimmerman et al. (1987)	2.70	2.55				2.09

Note: Comparative survey of mean interpeak latency values of ABR waves in term infants to adulthood. Mean interpeak latency values are in msec; SDs (in parentheses). Click stimuli were used in all the above studies. Click rate ranged from 10 to 23 per sec. M=month. Y= year. Term is defined as 37-43 weeks GA. Adults were defined by investigators as > 15 years of age. In some studies interpeak latency values for children and adults were grouped together (ranging from 5-33 years of age). In these cases ([a], [b], and [d]), mean interpeak and SD values were defined in the Table above as adult. Discrepancies across studies may be due to variations in equipment, methods and recording conditions. Data are displayed in Figure 6. Age ranges displayed were based on infant responses reaching adult value by two years of age. Abbreviations and footnotes also used in Tables 14 and 15.

[c] Means and SDs of interpeak latency values of infants in the mature control group.

[e] Mean interpeak latency values published in Starr & Amlie (1981).

Table 14 Mean Interpeak Latency Values of ABR Wave III-V in Term Infants to Adulthood

Wave III-V						
Study	**Term**	**3M**	**18M-2Y**	**3Y**	**5Y**	**Adult**
Beiser et al. (1985)	2.32 (0.24)	2.05 (0.22)	1.96 (0.20)			1.93 (0.08)
Chiappa et al. (1979)						1.90 (0.18)
Eggermont & Salamy (1988)	2.31 (0.44)	2.22 (0.42)	2.02 (0.16)	2.00 (0.31)	1.83 (0.24)	1.83 (0.24)
Eldredge & Salamy (1996)	2.26 (0.25)					
Gorga et al. (1989)		2.13 (0.22)	1.96 (0.20)	1.94 (0.17)		
Jiang et al. (2004)	2.18 (0.11)					
Jiang et al. (1998)	2.17 (0.11)					1.86 (0.14)
Jiang et al. (2002)	2.16 (0.11)					
Jiang & Wilkinson (2008)	2.18 (0.11)					
Jiang et al. (1991)	2.06 (0.20)	1.99 (0.14)	1.82 (0.16)	1.82 (0.15)	1.76 (0.16)	1.84 (0.18)
Krumholz et al. (1985)	2.18 (0.27)					1.89 (0.16)
Lima et al. (2008)						1.81 (0.22)
Lina-Granade et al. (1993)	2.35 (0.29)					1.83 (0.15)
Morgan et al. (1987) [b]	2.17 (0.27)					1.74 (0.21)
Pasman et al. (1996)	2.04 (0.37)					
Pasman et al. (1992)	2.08 (0.33)	2.10 (0.25)				

Table 14 continued.

Rotteveel et al. (1985)	2.16	2.00				
Rotteveel, Colon et al. (1986a)	2.07 (0.34)	2.12 (0.24)				
Rotteveel, de Graaf et al. (1987a)	2.09 (0.40)	2.16 (0.30)				
Salamy et al. (1982)	2.30 (0.39)	2.18 (0.23)		1.91 (0.19)		1.93 (0.18)
Scherg & Speulda (1982)						1.91 (0.14)
Stockard et al. (1978)						1.89
Stockard et al. (1979)	2.13 (0.23)					1.94 (0.38)
Stockard & Westmoreland (1981)	2.15 (0.23)					
Zimmerman et al. (1987)	2.12	1.98				1.74

Table 15 Mean Interpeak Latency Values of ABR Wave I-V in Term Infants to Adulthood

Wave I-V						
Study	**Term**	**3M**	**18M-2Y**	**3Y**	**5Y**	**Adult**
Beiser et al. (1985)	5.12 (0.28)	4.94 (0.21)	4.28 (0.25)			4.16 (0.12)
Chiappa et al. (1979)						4.00 (0.23)
Despland & Galambos (1982)	5.07 (0.41)					
Eggermont & Salamy (1988)	5.14 (0.40)	4.71 (0.27)	3.21 (0.21)	4.16 (0.29)	4.02 (0.16)	4.08 (0.25)
Eldredge & Salamy (1996)	4.95 (0.24)					
Fawer & Dubowitz (1982)	4.87 (0.27)					
Gorga et al. (1989)		4.66 (0.29)	4.14 (0.25)	4.12 (0.25)		
Jiang et al. (2004)	4.96 (0.17)					
Jiang et al. (1998)	4.96 (0.20)					4.01 (0.15)
Jiang et al. (2002)	4.90 (0.17)					
Jiang & Wilkinson (2008)	4.93 (0.20)					
Jiang et al. (1991)	4.89 (0.24)	4.80 (0.24)	4.21 (0.21)	4.04 (0.20)	3.96 (0.21)	3.94 (0.18)
Krumholz et al. (1985)	4.92 (0.29)					3.99 (0.20)
Lima et al. (2008)						3.87 (0.26)
Lina-Granade et al. (1993)	4.81 (0.58)					3.98 (0.18)
Mochizuki et al. (1988) [a]	5.18 (0.26)	4.96 (0.20)	4.35 (0.23)	4.31 (0.20)	4.12 (0.18)	4.14 (0.18)

Table 15 continued.

Morgan et al. (1987) [b]	4.88 (0.39)					3.83 (0.24)
Pasman et al. (1996)	4.98 (0.29)					
Pasman et al. (1992)	4.95 (0.25)	4.57 (0.22)				
Rotteveel et al. (1985)	4.88	4.64				
Rotteveel, Colon et al. (1986a)	4.95 (0.24)	4.58 (0.22)				
Rotteveel, Colon et al. (1987a) [c]	5.00 (0.20)	4.60 (0.20)				
Rotteveel, de Graaf et al. (1987a)	4.91 (0.31)	4.68 (0.24)				
Salamy & McKean (1976) [d]	5.12 (0.29)	4.67 (0.35)				3.99 (0.21)
Salamy et al. (1978)	4.99 (0.31)	4.73 (0.12)		4.18 (0.43)		3.88 (0.27)
Salamy et al. (1982)	5.09 (0.42)	4.72 (0.25)		4.03 (0.23)		4.08 (0.25)
Scherg & Speulda (1982)						4.05 (0.21)
Starr et al. (1977) [e]	5.00					4.00
Stockard et al (1983)	4.90 (0.28)					
Stockard et al. (1978)						4.00
Stockard et al. (1979)	4.92 (0.26)					4.02 (0.24)
Stockard & Westmoreland (1981)	4.90 (0.27)					
Zimmerman et al. (1987)	4.82	4.53				3.83

Response amplitudes of ABR waves also exhibit independent age-related changes (cf. Tables 9, 16 and Figures 4, 7). These findings complement latency findings in the above studies, which have revealed the development of the brainstem is incomplete at birth. In general, all ABR wave peaks showed an increase in amplitude as a function of age (Eggermont & Salamy, 1988; Krumholz et al., 1985; Mochizuki et al., 1982; Rotteveel, de Graaf et al., 1987a; Salamy, Fenn, & Bronshvag, 1979; Salamy et al., 1982; Salamy et al., 1978). Although adult configuration replaces the infant response by three to six months of age, amplitude peaks for ABR waves I and III were found to reach adult value by nine months of age, whereas amplitude peaks for ABR wave V were found to reach adult value by 2 to 3 years of age (Mochizuki et al., 1982). However, because amplitude measures are susceptible to substantial variability--due to stimulus (e.g., intensity, rate and stimulus frequency) and extraneuronal influences (e.g., resistance-capacitive properties of the skull)--their clinical usefulness is limited (Hecox & Burkard, 1982; Salamy, et al., 1979; Schwartz et al., 1994; Silman & Silverman, 1991; Starr et al., 1977).

Table 16 Mean Amplitude and Ratio Values of ABR Waves in term Infants to Adulthood

	Wave I Amplitude Values				Wave III				Wave V				V-I Interpeak Ratio					
Study	**Term**	**3M**	**6M**	**Adult**	**Term**	**3M**	**6M**	**Adult**	**Term**	**3M**	**6M**	**Adult**	**Term**	**3M**	**2Y**	**3Y**	**5Y**	**Adult**
Chiappa et al. (1979)				0.28 (0.14)				0.23 (0.12)				0.43 (0.16)						
Eggermont & Salamy (1988)													1.31 (0.86)	1.43 (0.75)	1.72 (0.47)	2.63 (2.35)	1.91 (0.58)	2.13 (1.26)
Jiang et al. (2004)	0.17 (0.05)				0.21 (0.06)				0.20 (0.06)				1.46 (0.93)					
Jiang et al. (1998)	0.15 (0.05)			0.11 (0.05)					0.19 (0.05)			0.30 (0.13)	1.58 (0.73)					3.29 (1.34)
Jiang et al. (2002)	0.20 (0.04)				0.21 (0.06)				0.19 (0.05)				1.03 (0.34)					
Jiang & Wilkinson (2008)	0.17 (0.06)				0.21 (0.06)				0.21 (0.06)				1.46 (0.93)					
Lasky (1984)	0.20 (0.10)			0.13 (0.04)	0.25 (0.08)			0.21 (0.05)	0.28 (0.13)			0.37 (0.11)						
Pasman et al. (1996)													1.52 (0.71)					
Pasman et al. (1992)									0.22 (0.08)	0.24 (0.09)			1.43 (0.67)	1.36 (0.69)				
Rotteveel, de Graaf et al. (1987a)	0.18 (0.07)	0.20 (0.09)			0.09 (0.06)	0.09 (0.08)			0.19 (0.07)	0.20 (0.09)			1.10 (0.50)	1.20 (0.60)				
Salamy et al. (1982) [a]	0.15 (0.60)	0.21 (0.11)	0.20 (0.01)	0.19 (0.10)	0.09 (0.04)	0.15 (0.07)	0.18 (0.12)	0.16 (0.09)	0.17 (0.06)	0.27 (0.11)	0.34 (0.20)	0.35 (0.13)	1.33 (0.86)	1.53 (0.81)				2.13 (1.26)
Salamy et al. (1978)	0.11 (0.03)	0.16 (0.05)	0.13 (0.07)	0.13 (0.06)	0.10 (0.04)	0.19 (0.09)	0.15 (0.06)	0.14 (0.04)	0.13 (0.05)	0.18 (0.09)	0.17 (0.08)	0.20 (0.08)						
Salamy et al. (1978)	0.11 (0.04)	0.14 (0.05)	0.13 (0.04)	0.12 (0.05)	0.09 (0.04)	0.17 (0.04)	0.17 (0.06)	0.12 (0.06)	0.11 (0.03)	0.16 (0.04)	0.19 (0.09)	0.21 (0.07)						

Note: Comparative survey of mean amplitude and ratio values of ABR waves in term infants and adults. Mean amplitude values are in μV; SDs (in parentheses). Click stimuli were used in all the above studies. Click rate ranged from 10 to 21.2 per sec. M=month. Y= year. Term is defined as 37-43 weeks GA. Adults were > 15 years of age. Discrepancies across studies may be due to variations in equipment, methods and recording conditions. Age ranges displayed were based on the ability to match data in the literature. Data are displayed in Figure 7, however it may not adequately demonstrate some developmental trends suggested in the literature.

[a] Mean amplitude and ratio values also published in Salamy (1984).

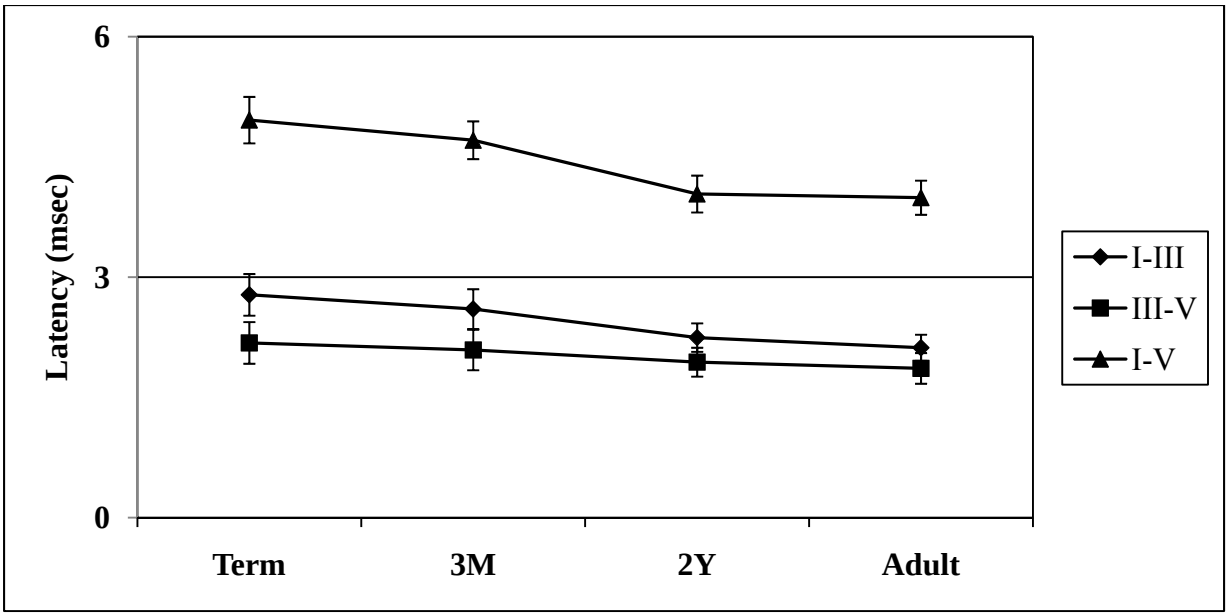


Figure 6 Summary of Interpeak Latency Values of ABR Waves

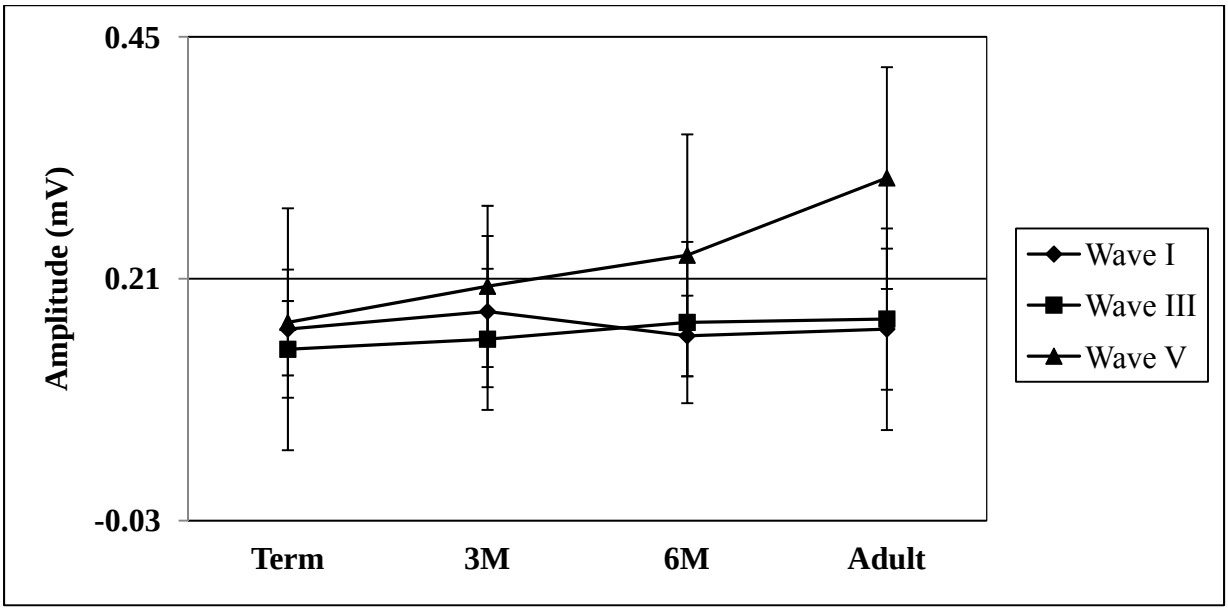


Figure 7 Summary of Amplitude Values of ABR Waves

In summary, differences in recording protocol notwithstanding, it is clear that there is a distinct maturation pattern for the ABR. Differential changes in ABR latency and amplitude reveal that auditory maturation involves both the peripheral (auditory nerve) and the central (lower brainstem) auditory structures. Overall, results of studies reveal that waveform morphology of an infant response reaches adult configuration between three and six month of age, whereas developmental changes in absolute and interpeak latency values gradually develop from peripheral to central, reaching adult values by approximately 18 months to two years of age (Fria & Doyle, 1984; Hecox & Galambos, 1974; Salamy & McKean, 1976) (cf. Figure 5 and 6).

3.4.1.2 MLR

The infant MLR is incomplete at birth and differs from an adult in virtually all measurement parameters. Reliable components of the MLR have been successfully recorded as early as the 27th week GA (Mendelson & Salamy, 1981; Rotteveel, Colon et al., 1987a; Rotteveel, Colon, Stegeman, & Visco, 1987b; Rotteveel, de Graaf, Stegeman, Colon, & Visco, 1987b; Rotteveel, Stegeman, de Graaf, Colon, & Visco, 1987) (cf. Table 17). N_a and P_a are the most reproducible MLR components in preterm infants. However, the infant response is typically characterized by a very broad-based waveform; the vertex-positive P_a being more prominent than its preceding negative wave N_a. The waveform morphology of an infant response is markedly different from those of an adult and reaches adult configuration after the first decade of life (McGee & Kraus, 1996) (cf. Table 18 and Figure 9).

In addition to the morphology of the infant response, the prevalence and stability of waves P_a and N_b show age dependency and increase in amplitude from preterm through adolescence (McGee & Kraus, 1996; Kraus et al., 1985; McPherson, Tures, & Starr, 1989; McRandle, Smith, & Goldstein, 1974; Mendel, Adkinson, & Harker, 1977; Mendelson &

Salamy, 1981; Schochat & Musiek, 2006; Tucker & Ruth, 1996). Furthermore, the majority of investigations have reported that response latency decreases as a function of maturation from preterm to term (Rotteveel, Colon et al., 1987a, 1987b; Rotteveel, Stegeman et al., 1987), and then remains fairly stable through adulthood (McPherson et al., 1989; Mendel et al., 1977; Mendelson & Salamy, 1981). Other investigations however, have reported response latency continually decreases from term infancy through adulthood (Tucker & Ruth, 1996) (cf. Figures 8 and 9).

Table 17 Mean Amplitude and Latency Values of MLR Waves in Preterm Infants

Study	27-29	30-31	32-33	34-35	36-37	38-39	40-43 GA
N_a Amplitude Values							
Rotteveel, Colon et al. (1987a)	0.17 (0.03)	0.20 (0.04)	0.25 (0.09)	0.26 (0.11)	0.23 (0.07)	0.30 (0.10)	0.31 (0.08)
Rotteveel, de Graaf et al. (1987b)	-0.80 (0.07)	-0.80 (1.10)	-0.80 (0.70)	-0.50 (0.90)	-0.60 (0.70)	-0.80 (0.70)	-0.60 (0.90)
Rotteveel, Stegeman et al. (1987)	-0.29 (0.21)	-0.28 (0.18)	-0.33 (0.19)	-0.37 (0.21)	-0.38 (0.24)	-0.40 (0.28)	-0.42 (0.16)
P_a							
Rotteveel, Stegeman et al. (1987)		0.08 (0.20)	-0.05 (0.20)	-0.05 (0.18)	0.09 (0.26)	0.07 (0.26)	-0.06 (0.15)
N_b							
Rotteveel, Colon et al. (1987a)		-0.05 (0.00)	-0.10 (0.07)	-0.03 (0.01)	-0.03 (0.03)	-0.05 (0.05)	-0.09 (0.09)
N_a Latency Values							
Mendelson & Salamy (1981)				24.50 (3.90)			
Rotteveel, Colon et al. (1987a)	28.00 (4.00)	27.00 (4.00)	22.00 (2.00)	21.00 (2.00)	20.00 (1.00)	20.00 (2.00)	19.00 (1.00)
Rotteveel, Colon et al. (1987b)	40.00	28.00	25.00 (2.00)	23.00 (2.00)	24.00 (5.00)	22.00 (2.00)	22.00 (4.00)
Rotteveel, de Graaf et al. (1987b)	36.00 (6.00)	28.00 (4.00)	25.00 (3.00)	25.00 (4.00)	23.00 (4.00)	23.00 (2.00)	22.00 (3.00)
Rotteveel, Stegeman et al. (1987)	31.20 (2.60)	27.40 (3.20)	22.10 (2.20)	21.20 (2.20)	19.30 (1.70)	19.00 (1.80)	18.80 (1.60)
P_a							
Mendelson & Salamy (1981)				34.50 (3.00)			
Rotteveel, Stegeman et al. (1987)	32.8	31.20 (4.70)	26.60 (2.60)	26.50 (1.70)	25.50 (2.70)	26.50 (2.40)	25.40 (2.00)

Table 17 continued.

N_b							
Mendelson & Salamy (1981)				44.40 (4.90)			
Rotteveel, Colon et al. (1987a)		40.00 (0.00)	35.00 (4.00)	38.00 (2.00)	32.00 (2.00)	32.00 (3.00)	29.00 (2.00)

Note: Comparative survey of mean amplitude and latency values of MLR waves in preterm infants. Mean amplitude values are in μV and latency values are in msec; SDs (in parentheses). Click stimuli were used in all the above studies. Click rate ranged from 4.5 to 9.7 per sec. GA=gestational age. Amplitude measurements were all baseline-to-peak. Discrepancies across studies may be due to variations in equipment, methods and recording conditions. Data for 30-31 GA are displayed in Figure 9.

Table 18 Mean Amplitude and Latency Values of MLR Waves in Term Infants and Adults

	N_a Amplitude Values		P_a		N_b	
Study	**Term**	**Adult**	**Term**	**Adult**	**Term**	**Adult**
McPherson et al. (1989)	0.31 (0.04)	0.42 (0.08)	0.12 (0.02)	0.42 (0.13)		0.05 (0.01)
Pasman et al. (1992)	-0.50 (0.16)					
Rotteveel, Colon et al. (1986b)	-0.38 (0.16)				-0.26 (0.13)	
Rotteveel, Colon et al. (1986c)	-0.40 (0.80)					
Rotteveel, Colon et al. (1987a)	-0.38 (0.16)					
Rotteveel, de Graaf et al. (1987b)	-0.50 (0.70)					
Rotteveel, Stegeman et al. (1987)	-0.42 (0.16)		-0.06 (0.15)			
	N_a Latency Values		P_a		N_b	
McPherson et al. (1989)	13.50 (0.70)	14.10 (1.10)	23.30 (2.30)	25.00 (1.50)		37.50 (1.50)
McRandle et al (1974)	17.20 (5.20)		28.20 (5.40)		35.20 (2.10)	
Mendel et al. (1977)	16.50	19.10	24.20	29.20	37.60	39.40
Mendelson & Salamy (1981)	22.31 (4.36)	21.06 (3.01)	31.98 (1.81)	30.60 (2.18)	46.10 (3.70)	42.86 (5.06)
Pasman et al. (1992)	18.6 (2.30)					
Rogers, Edwards, Henderson-Smart & Pettigrew (1989)	19.3 (1.70)	18.4 (1.10)	36.8 (3.60)	30.5 (2.30)	47.3 (3.90)	41.3 (3.80)
Rotteveel et al. (1985)	18.00					
Rotteveel, Colon et al. (1986b)	18.40 (1.40)				28.30 (2.60)	

Table 18 continued.

Rotteveel, Colon et al. (1986c)	26.00 (4.00)					
Rotteveel, Colon et al. (1987a)	18.00 (1.00)					
Rotteveel, Colon et al. (1987b)	26.00 (4.00)					
Rotteveel, de Graaf et al. (1987b)	22.00 (4.00)					
Rotteveel, Stegeman et al. (1987)	18.8 (1.60)		25.4 (2.00)			

Note: Comparative survey of mean amplitude and latency values of MLR waves in term infants and adults. Mean amplitude values are in μV and latency values are in msec; SDs (in parentheses). Click stimuli were used in all of the above studies. Click rate ranged from 4.5 to 15 per sec. Y= year. Term is defined as 39-43 weeks GA. Adults were > 18 years of age. Amplitude measurements were all baseline-to-peak. Discrepancies across studies may be due to variations in equipment, methods and recording conditions. To demonstrate the increase in amplitude that occurs from term to adolescence, N_aP_a amplitude data (not shown in Table, Tucker et al., 1996) are displayed in Figure 8. Latency was measured with respect to the baseline voltage. Latency data are displayed in Figure 9 (with additional values not shown in Table, Tucker et al., 1996). Dashes in Figures indicate data not reported. Age ranges displayed were based on the availability of data in the literature.

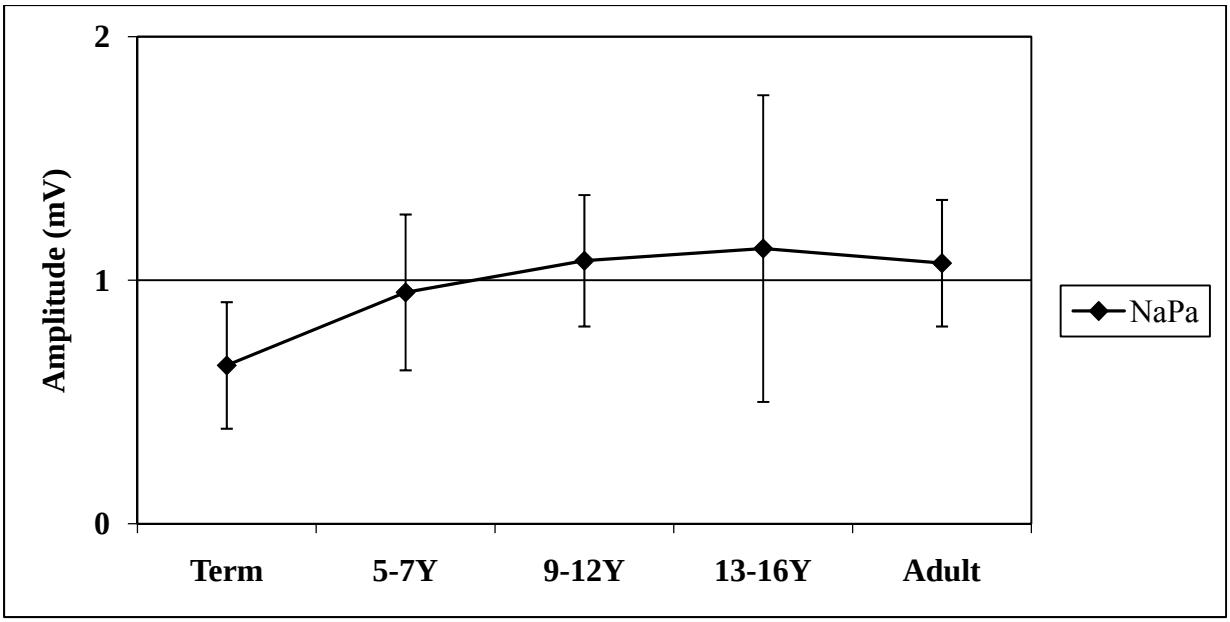


Figure 8 Summary of Amplitude Values of N_aP_a

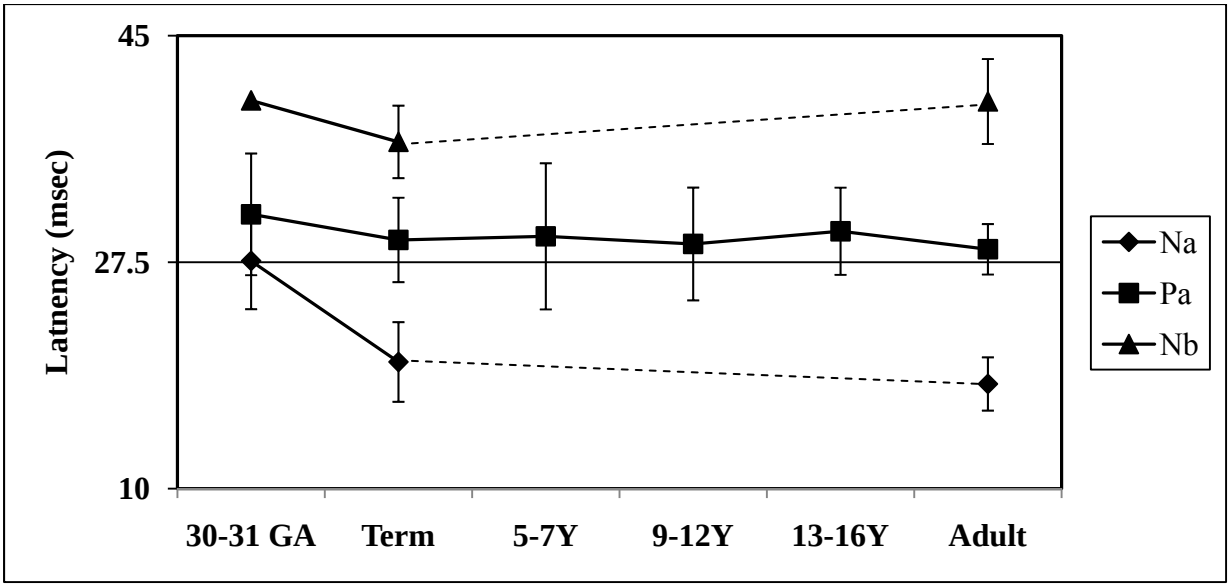


Figure 9 Summary of Latency Values of MLR Waves

Systematic changes that occur in the maturing MLR may be attributed to the development of the temporal lobe and the auditory thalamo-cortical pathway, maturational changes in sleep--in which detectability during an unfavorable sleep stage (4^{th}) improves with age--or an interaction of both (Kraus et al., 1994). Thus, researchers suggest the MLR reflects the interaction of cortical and subcortical generators of both nonprimary and primary auditory pathways. The developments of the nonprimary components (e.g., reticular formation and multi-sensory divisions of the thalamus) of the MLR seem to develop early and are susceptible to sleep stage; whereas the primary components (e.g., primary auditory cortex, thalamo-cortical projections and the lemniscal pathway) of the MLR develop later and are reliably detected across all sleep stages (McGee & Kraus, 1996).

In summary, the developmental aspects of the MLR appear to be related not only to changes in response amplitude and latency, but also to changes in the stability of its response. Overall, results of studies reveal a long developmental time course in which waveform morphology of an infant response reaches adult configuration just after the first decade of life.

3.4.1.3 LLR

The infant LLR is incomplete at birth and differs from an adult in the morphology and in the amplitude and latency of its response. Components of the LLR have to some extent been described in preterm infants as early as the 25^{th} week estimated GA (Weitzman & Graziani, 1968; Weitzman, Graziani, & Duhamel, 1967). However, developmental features with respect to all components of the LLR have been successfully recorded as early as the 27^{th} week GA (Rotteveel, Colon et al., 1987b; Rotteveel, de Graaf et al,1987b) (cf. Table 19). In the premature infant the major component is classified as a premature N_1 component, which becomes less prominent as the infant approaches 40 weeks GA. Premature components of the LLR gradually

develop into more mature waveforms around three months after term date (Rotteveel et al., 1985). At full-term, the infant LLR is typically characterized by a broad vertex-positive P_2 followed by the intervening negative trough N_2 (Rapin & Graziani, 1967; Weitzman & Graziani, 1968). Although the waveform morphology of an infant response is markedly different from those of an adult, the infant response reaches adult-like between three and six months of age (Davis & Onishi, 1969; Kurtzberg, Hilpert, Kreuzer & Vaughan, 1984; Steinschneider & Dunn, 2002; Vaughan & Kurtzberg, 1989) and continues to mature through adolescence (Courchesne, 1978).

Table 19 Mean Amplitude and Latency Values of LLR Waves in Preterm Infants

Study	27-29	30-31	32-33	34-35	36-37	38-39	40-43 GA
P_1 Amplitude Values							
Rotteveel, de Graaf et al. (1987b)	-0.00 (0.10)	-0.10 (0.50)	0.20 (1.20)	0.30 (0.60)	0.50 (0.70)	1.00 (0.80)	0.70 (0.80)
P_2							
Rotteveel, Colon et al. (1987b)	-.80	-1.00 (0.50)	-1.40 (0.20)	-1.60 (0.30)	-0.80 (0.60)	-0.30 (0.50)	0.30 (0.10)
Rotteveel, de Graaf et al. (1987b)	-1.20 (0.40)	-2.30 (1.80)	-1.60 (1.30)	-1.30 (1.30)	-0.10 (0.80)	0.40 (1.00)	1.00 (0.70)
N_2							
Rotteveel, Colon et al. (1987b)	-1.60	-2.40 (1.20)	-2.90 (0.90)	-2.90 (0.90)	-1.70 (0.40)	-1.00 (0.70)	-0.70 (0.30)
Rotteveel, de Graaf et al. (1987b)	-2.70 (0.70)	-3.90 (2.90)	-4.50 (1.90)	-3.30 (1.80)	-2.40 (1.90)	-1.50 (1.10)	-0.90 (0.90)
P_1 Latency Values							
Rotteveel, Colon et al. (1987b)	100.0	104.00 (17.00)	81.00 (7.00)	83.00 (8.00)	90.00 (10.00)	80.00 (8.00)	78.00 (8.00)
Rotteveel, de Graaf et al. (1987b)	84.00 (6.00)	104.00 (17.00)	96.00 (17.00)	91.00 (15.00)	89.00 (18.00)	78.00 (13.00)	77.00 (11.00)
N_1							
Rotteveel, Colon et al. (1987b)				140.0	148.0 (17.00)	136.0 (9.00)	130.0 (8.00)
P_2							
Rotteveel, Colon et al. (1987b)	192.0	156.0 (23.00)	167.0 (15.00)	172.0 (16.00)	178.0 (13.00)	117.0 (9.00)	172.0 (12.00)
Rotteveel, de Graaf et al. (1987b)	196.0 (6.00)	188.0 (28.00)	187.0 (17.00)	190.0 (15.0)	179.0 (17.00)	179.0 (20.00)	184.0 (21.00)

Table 19 continued.

N_2							
Rotteveel, Colon et al. (1987b)	256.0	234.0 (37.00)	258.0 (15.00)	246.0 (27.00)	235.0 (19.00)	249.0 (9.00)	250.0 (21.00)
Rotteveel, de Graaf et al. (1987b)	255.0 (15.00)	256.0 (26.00)	258.0 (22.00)	248.0 (21.00)	235.0 (23.00)	249.0 (35.00)	357.0 (51.00)

Note: Comparative survey of mean amplitude and latency values of MLR waves in preterm infants. Mean amplitude values are in μV and latency values are in msec; SDs (in parentheses). Click stimuli were used in the above studies. Clicks were presented at a mean rate of 0.5 per sec. GA = gestational age. Amplitude measures were all baseline-to-peak. Latency was measured with respect to baseline voltage. All measurements were based on C3´-A1 derivation.

Results of studies suggest that age differentially affects response measurements for various components of the LLR from infancy through adolescence. There exists, however, considerable variability among investigators about the developmental time course of the response amplitude for each LLR component (cf. Table 20). A number of investigators have reported a systematic decrease in P_1 amplitude as a function of age (Cunningham, Nicol, Zecker, & Kraus, 2000; Gilley, Sharma, Dorman, & Martin, 2005; Kraus et al., 1993; Oades, Dittmann-Balcar, & Zerbin, 1997; Ponton, Eggermont, Kwong, & Don, 2000; Poulsen, Picton, & Paus, 2009; Satterfield, Schell, Backs, & Hidaka, 1984; Wunderlich, Cone-Wesson, & Shepherd, 2006). Likewise, published findings have also shown an age-related decrease in N_1 amplitude as a function of age (Gilley, Sharma, Dorman, & Martin, 2005; Ponton et al., 2000; Sharma, Kraus, McGee, & Nicol, 1997). However, other investigations have either shown an age-related increase in N_1 amplitude (Anderer, Semlitsch, & Saletu, 1996; Cunningham et al., 2000; Pfefferbaum, Ford, Wenegrat, Roth, & Kopell, 1984; Poulsen et al., 2009; Satterfield et al., 1984; Takeshita et al., 2002; Wunderlich et al., 2006) or have shown a no relation between N_1 amplitude and age (Johnson, 1989; Pfefferbaum, Ford, Roth, & Kopell, 1980; Picton, Stuss, Champagne, & Nelson, 1984; Tonnquist-Uhlén, Borg, & Spens, 1995). Similarly, published findings have shown either an age-related decrease in P_2 amplitude (Ponton et al., 2000; Poulsen et al., 2009; Satterfield et al., 1984; Sussman, Steinschneider, Gumenyuk, Grushko, & Lawson, 2008), an increase in P_2 amplitude (Anderer et al., 1996; Barnet & Lodge, 1967; Johnstone, Barry, Anderson, & Coyle, 1996; Kraus et al., 1993; Oades, et al., 1997; Pfefferbaum, et al., 1980; Pfefferbaum et al., 1984; Wunderlich et al., 2006), or have shown no variation in P_2 amplitude as a function of age (Johnson, 1989). Furthermore, studies have shown either an age-related decrease in N_2 amplitude (Anderer et al., 1996; Cunningham et al., 2000; Enoki, Sanada,

Yoshinaga, Oka, & Ohtahara, 1993; Friedman, Brown, Cornblatt, Vaughan, & Erlenmeyer-Kimling, 1984; Johnstone et al., 1996; Oades, et al., 1997; Poulsen et al., 2009; Satterfield et al., 1984; Takeshita et al., 2002; Wunderlich et al., 2006) or have shown no relation between N_2 amplitude and age (Johnson, 1989).

Moreover, studies have shown either an age related decrease in N_1P_2 amplitude (Barnet, Ohlrich, Weiss, & Shanks, 1975; Satterfield et al., 1984), an increase in N_1P_2 amplitude (Gilley et al., 2005; Goodin, Squires, Henderson, & Starr, 1978; Martin, Barajas, Fernandez, & Torres, 1988; Shucard, Shucard, & Thomas, 1987), or have shown no clear age-related changes in N_1P_2 amplitude as a function of age (Courchesne, 1978; Ohlrich & Barnet, 1972) (cf. Table 21).

It is also difficult to extract a consistent pattern of age-related latency changes for each LLR component (cf. Table 22). Published findings have shown either an age-related decrease in P_1 latency (Cunningham et al., 2000; Gilley et al., 2005; Kraus et al., 1993; Oades et al., 1997; Ohlrich, Barnet, Weiss, & Shanks, 1978; Sharma et al., 1997; Ponton et al., 2000, Ponton, Eggermont, Khosla, Kwong, & Don, 2002; Poulsen et al., 2009; Sharma, Dorman, & Spahr, 2002; Sussman, et al., 2008), an increase in P_1 latency (Satterfield et al., 1984), or have shown no relation between P_1 latency and age (Barnet et al., 1975). Likewise, published findings have shown either an age-related decrease in N_1 latency (Cunningham et al., 2000; Johnstone et al., 1996; Kraus et al., 1993; Martin et al., 1988; Oades et al., 1997; Paetau, Ahonen, Salonen, & Sams, 1995; Ponton et al., 2002; Ponton et al., 2000; Poulsen et al., 2009; Rojas, Walker, Sheeder, Teale, & Reite, 1998; Sharma et al., 1997; Shucard, Shucard, & Cummins, 1981; Shucard et al., 1987; Takeshita et al., 2002; Tonnquist-Uhlén et al., 1995; Weitzman & Graziani, 1968), an increase in N_1 latency (Satterfield et al., 1984), or have shown little or no variation in N_1 latency as a function of age (Anderer et al., 1996; Barnet et al., 1975; Courchesne, 1978;

Davis & Onishi, 1969; Johnson, 1989; Ohlrich et al., 1978; Onishi & Davis, 1969; Pfefferbaum et al., 1980; Pfefferbaum et al., 1984; Picton et al., 1984).

Moreover, considerable variability also exists across studies in which the developmental time course of P_2 and N_2 latency were investigated. Published findings have shown either an age-related decrease P_2 latency (Barnet & Lodge, 1967; Barnet et al., 1975; Oades et al., 1997; Ohlrich & Barnet, 1972; Ohlrich et al., 1978; Shucard, et al., 1981; Shucard et al., 1987; Weitzman & Graziani, 1968), an increase in P_2 latency (Barrett, Neshige, & Shibasaki, 1987; Gilley et al., 2005; Kraus et al., 1993; Martin et al., 1988; Pfefferbaum et al., 1980; Picton et al., 1984; Satterfield et al., 1984; Wunderlich et al., 2006), or have shown no significant changes in P_2 latency as a function of age (Anderer et al., 1996; Courchesne, 1978; Davis & Onishi, 1969; Johnson, 1989; Johnstone et al., 1996; Onishi & Davis, 1969; Ponton et al., 2000, Ponton et al., 2002; Poulsen et al., 2009). Likewise, published findings have shown either an age-related decrease in N_2 latency (Barnet et al., 1975; Cunningham et al., 2000; Enoki et al., 1993; Goodin et al., 1978; Oades, et al., 1997; Ohlrich & Barnet, 1972; Ohlrich et al., 1978; Poulsen et al., 2009; Shucard, et al., 1981; Shucard et al., 1987), an increase in N_2 latency (Anderer et al., 1996; Barrett et al., 1987; Martin et al., 1988; Picton et al., 1984; Ponton et al., 2000, Ponton et al., 2002; Satterfield et al., 1984), or have shown little or no variation in N_2 latency as a function of age (Davis & Onishi, 1969; Friedman et al., 1984, Johnson, 1989; Johnstone et al., 1996; Onishi & Davis, 1969; Takeshita et al., 2002; Weitzman & Graziani, 1968).

Investigators speculate that the maturational time course for the LLR may not follow a hierarchical-sequential model with respect to latency (Kraus et al., 1993; Ponton et al., 2000). Spatiotemporal aspects, dipole source modeling and AEP data analyzed via intraclass correlation (ICC) distinguished four developmental periods: between 36 and 41 weeks CA, between 5 and

12 years, between 13 and 16 years, and adulthood (Bishop, Hardiman, Uwer, & von Suchodoletz, 2007; Pasman, Rotteveel, Maassen, & Visco, 1999). These analyses revealed that the maturation for P_2 latency is short, becoming adult-like by 5 years of age or earlier, whereas maturation for P_1, N_1 and N_2 latency is long, becoming adult-like by 15-16 years of age. In contrast, P_1, N_1, P_2, and N_2 amplitudes substantially decline after 10 years of age, becoming adult-like by approximately 17 years of age (Ponton et al., 2000, Ponton et al., 2002). Differences in these aspects may be attributed to increased myelination and neuronal maturation within the primary and secondary auditory cortex, interactions between state of arousal and response latency and amplitude, or both (Goodin et al., 1978; Ohlrich & Barnet, 1972; Ponton et al., 2000).

From this aggregate of information, it is difficult to extract any meaningful conclusions regarding the maturation sequence of the LLR components for a number of reasons. Differences in study design (e.g., small numbers of participants, age ranges of subject groups) and in the methods employed (e.g., stimuli, electrode configurations) make it difficult to compare results across studies with any confidence. Because of these inter-study differences there were only a few studies that could be reasonably matched to produce Tables 20, 21, and 22, and to create Figure 10 (may not display some developmental trends suggested in the literature). However, other reviews are available to the reader which analyze component values using different stimuli, scalp regions and age ranges, namely, Anderer et al. (1996), Cunningham et al. (2000), Kraus et al. (1993), Ponton et al. (2000 and 2002), Satterfield et al. (1984), and Sharma et al. (1997).

Table 20 Mean Amplitude Values of LLR Waves in Term Infants to Adulthood

P_1 Amplitude Values					**N_1**			
Study	**Term**	**2Y**	**4-7Y**	**Adult**	**Term**	**2Y**	**4-7Y**	**Adult**
Click								
Pasman et al. (1992)					0.20 (0.90)			
Rotteveel, Colon et al. (1986c)	0.80 (0.60)				0.30 (1.00)			
Rotteveel, de Graff et al. (1987b)	0.70 (0.80)				-0.30 (0.70)			
Tone Burst								
Wunderlich et al. (2006) [400 Hz]	1.70 (1.30)	3.00 (1.50)	2.10 (0.30)	1.10 (0.80)	-1.50 (0.50)	-3.40 (1.80)	-3.40 (2.00)	-5.60 (1.70)
Wunderlich et al. (2006) [3 kHz]	1.20 (0.70)	4.30 (3.10)	1.90 (0.30)	1.60 (1.00)	-1.70 (0.80)	-2.40 (1.70)	-3.70 (2.70)	-4.60 (0.90)
P_2 Amplitude Values					**N_2**			
Click								
Pasman et al. (1992)	2.50 (1.70)				-2.30 (1.90)			
Rotteveel, Colon et al. (1986c)	1.10 (1.20)				-0.60 (1.90)			
Rotteveel, Colon et al. (1987b)	1.10 (1.20)				-0.60 (1.90)			
Rotteveel, de Graff et al. (1987b)	1.00 (0.70)				-0.90 (0.90)			
Tone Burst								
Wunderlich et al. (2006) [400 Hz]	3.10 (1.40)	3.80 (1.10)	4.60 (2.70)	6.70 (1.80)	-3.49 (0.55)	-4.00 (2.50)	-4.00 (1.80)	-2.70 (1.50)
Wunderlich et al. (2006) [3 kHz]	1.80 (0.80)	5.30 (3.60)	3.10 (2.10)	5.10 (1.00)	-2.20 (0.67)	-4.20 (2.60)	-2.70 (1.20)	-2.70 (1.50)

Note: Comparative survey of mean amplitude values of LLR waves in term infants to adulthood. Mean amplitude values are in μV; SDs (in parentheses). Stimuli were presented at a mean rate of 0.5 per sec. or with a median ISI of 3100 msec. Y= year. Term is defined as 37-43 weeks GA. Adults were > 18 years of age. Amplitude measures were all baseline-to-peak. Age ranges displayed were based on the ability to match data in the literature.

Table 21 Mean Amplitude of N_1P_2 in Term Infants to Adulthood

N_1P_2 Amplitude Values								
Study	**Term**	**6M**	**12M**	**2Y**	**6-7Y**	**9-10Y**	**12-14Y**	**Adult**
Click								
Barnet et al. (1975)		5.60 (2.80)	5.80 (2.90)	10.30 (7.70)				
McRandle et al. (1974)	3.60 (1.90)							
Ohlrich & Barnet (1972)		8.00 (5.10)	11.00 (8.80)					
Filtered Click								
Martin et al. (1988)					2.53 (1.86)	3.43 (2.83)	7.69 (3.87)	7.61 (2.58)
Shucard et al. (1987)		24.58 (9.59)						20.16 (6.32)
Tone Burst								
Durrant (1987a)								12.00 (3.70)
Pattern-Reversal								
Durrant (1987a)								14.50 (5.10)

Note: Comparative survey of mean amplitude values of N_1P_2 in term infants to adulthood. Mean amplitude values are in μV; SDs (in parentheses). Stimuli were presented at variable rates. M=months, Y=year. Term = full term GA. Adults were > 18 years of age. Age ranges displayed were based on the ability to match data in the literature.

Table 22 Mean Latency Values of LLR Waves in Term Infants to Adulthood

P_1 Latency Values							**N_1**					
Study	**Term**	**6M**	**2Y**	**6-7Y**	**12-14Y**	**Adult**	**Term**	**6M**	**2Y**	**6-7Y**	**12-14Y**	**Adult**
Click												
Barnet et al (1975)		99.00 (27.00)	76.00 (19.00)					139.0 (31.00)	91.00 (26.00)			
Engel (1971)							144.0 (28.00)					
McRandle et al. (1974)	107.0 (32.00)						172.0 (31.00)					
Monod & Garma (1971)	65.00						136.0 (11.00)					
Ohlrich & Barnet (1972)		89.00 (39.00)						120.0 (44.00)				
Pasman et al. (1992)							140.0 (25.00)					
Rotteveel, Colon et al. (1986c)	146.0 (20.00)						143.0 (28.00)					
Rotteveel, Colon et al. (1987b)	68.00 (15.00)						143.0 (28.00)					
Rotteveel, de Graff et al. (1987b)	77.00 (11.00)						128.0 (17.00)					
Filtered Click												
Davis et al. (1966)	59.00 (9.00)											107.0 (13.00)
Martin et al. (1988)										119.5 (33.25)	106.1 (14.20)	103.8 (12.20)
Shucard et al. (1981) [a]						50.90		135.8				93.80
Shucard et al. (1987)						50.90 (13.50)		135.8 (13.30)				93.80 (5.60)

Table 22 continued.

Tone Burst												
Durrant (1987a)						50.00 (12.00)						99.00 (9.00)
Wunderlich et al. (2006) [400 Hz]	78.00 (5.30)		89.60 (36.00)	85.70 (46.10)		53.40 (13.40)	185.9 (47.80)		142.7 (11.40)	173.2 (42.80)		107.7 (18.30)
Wunderlich et al. (2006) [3 kHz]	85.70 (9.50)		79.10 (27.30)	77.40 (24.40)		56.00 (14.30)	154.1 (41.90)		150.5 (19.30)	157.8 (44.00)		108.8 (16.50)
Pattern-Reversal												
Durrant (1987a)						67.00 (5.00)						119.0 (9.00)
P_2 Latency Values							**N_2**					
Study	**Term**	**6M**	**2Y**	**6-7Y**	**12-14Y**	**Adult**	**Term**	**6M**	**2Y**	**6-7Y**	**12-14Y**	**Adult**
Click												
Barnet & Lodge (1967)	228.2											
Barnet et al (1975)		199.0 (28.00)	151.0 (22.00)					442.0 (42.00)	323.0 (59.00)			
Engel (1971)	249.0 (28.00)											
McRandle et al. (1974)	239.0 (25.00)						321.0 (46.00)					
Monod & Garma (1971)	230.0 (19.00)						533.0 (25.00)					
Ohlrich & Barnet (1972)		193.0 (29.00)						425.0 (38.00)				
Pasman et al. (1992)	209.0 (22.00)						344.0 (54.00)					
Rotteveel et al. (1985)	192.0											
Rotteveel, Colon et al. (1986c)	209.0 (21.00)						363.0 (59.00)					
Rotteveel, Colon et al. (1987b)	209.0 (21.00)						363.0 (59.00)					
Rotteveel, de Graff et al. (1987b)	184.0 (21.00)						357.0 (51.00)					

Table 22 continued.

Filtered Click												
Davis et al. (1966)						188.0 (22.00)						
Martin et al. (1988)				161.4 (41.18)	163.8 (16.71)	170.1 (16.15)				209.9 (36.44)	230.8 (19.27)	218.2 (32.16)
Shucard et al. (1981) [a]		206.8				158.8		300.2				247.1
Shucard et al. (1987)		206.8 (21.30)				158.8 (6.70)		300.2 (30.00)				247.1 (26.50)
Tone Burst												
Durrant (1987a)						169.0 (9.00)						
Wunderlich et al. (2006) [400 Hz]	214.0 (16.10)		297.3 (58.50)	254.4 (44.90)		175.8 (28.80)	373.1 (39.60)		396.5 (68.00)	391.7 (50.80)		290.6 (40.80)
Wunderlich et al. (2006) [3 kHz]	240.8 (46.60)		255.5 (56.40)	261.1 (63.50)		176.9 (27.40)	393.4 (96.80)		372.8 (52.30)	376.6 (78.20)		311.6 (29.70)
Pattern-Reversal												
Durrant (1987a)						195.0 (10.00)						

Note: Comparative survey of mean latency values of LLR waves in term infants to adulthood. Mean latency values are in msec; SDs (in parentheses). Click rate ranged from 0.5 per sec. to 1 every 20 sec. Term is defined as 37-43 weeks GA. Adults were typically defined by investigators as > 18 years of age. Data are displayed in Figure 10. Dashes indicate latencies not reported. Age ranges displayed were based on the ability to match data in the literature.
[a] Latency values published in Shucard et al. (1987).

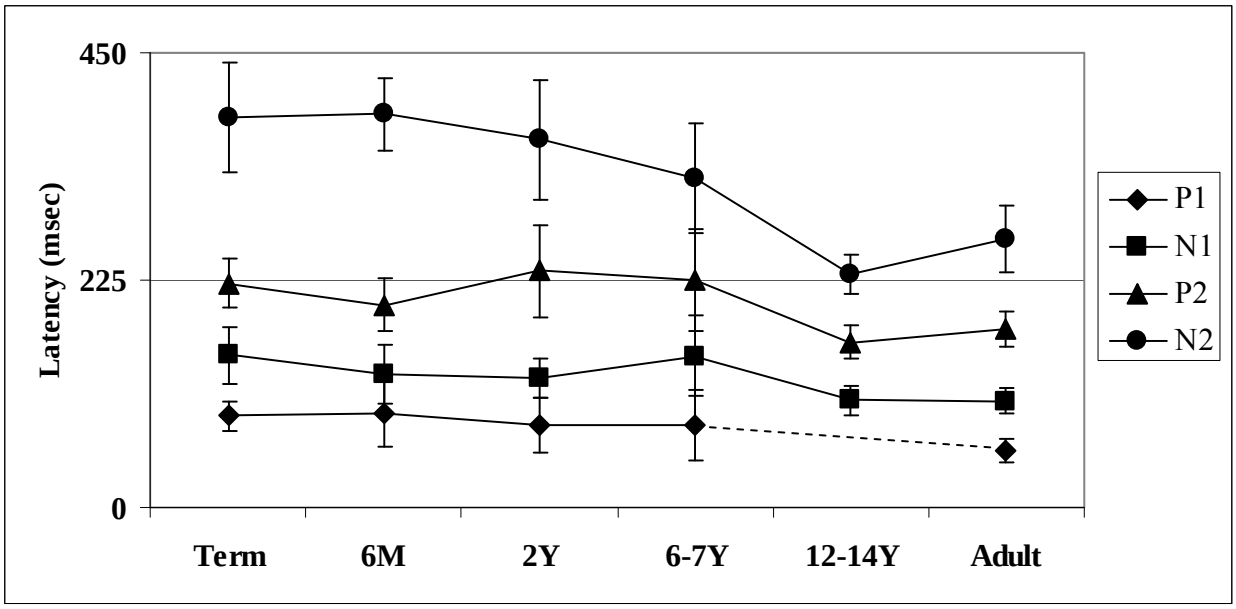


Figure 10 Summary of Latency Values of LLR Waves

In summary, the relative behavior in terms of maturation of the LLR components appears to be related to changes in the amplitude and latency of its response. Results from studies suggest that age differentially affects response measurements for various components of the LLR from infancy through adolescence. Thus, a long developmental process underlies the maturation of the LLR, in which amplitude and latency continue to mature nearly into the second decade of life.

3.4.2 Evoked by Steady-state stimuli

3.4.2.1 ASSR

The infant ASSR is complete at birth, but differs from that of an adult in thresholds, amplitude and detectability of its response. ASSRs have been successfully recorded as early as the 31st week estimated GA (Cone-Wesson et al., 2002). Response amplitudes significantly increase as a

function of age through the neonatal and early infant period (John, Brown, Muir, & Picton, 2004; Lins et al., 1996; Maurizi et al., 1990; Rojas et al., 2006; Savio, Cárdenas, Pérez Abalo, González, & Valdés, 2001), with the greatest growth occurring between 0 and six months (Savio et al., 2001). Also, clear age-related changes in response thresholds are evident during the first year of life (Rance & Tomlin, 2006; Savio et al., 2001). Infant response amplitudes are typically one third to one half the size of an adult's response by 11 months of age (Lins et al., 1996). Although it is unclear what age the infant response becomes similar to that of an adult, Pethe et al. (2002) suggests that the optimal modulation frequency changes from 80 Hz to 40 Hz at 13 years of age. These developmental changes in response amplitude may be attributed to either the developmental sequence that underlies the maturation of the ASSR, the complexities of inherent physical and physiological mechanisms of the ASSR that occur with age, or an interaction of both (Pastor et al., 2002; Savio et al., 2001).

Detectability of the 80-Hz ASSR in newborns and early infants has varied across studies. Responses were evoked by approximately 50 to 90% of newborns at 0.5 kHz, (Cone-Wesson et al., 2002; John et al., 2004; Lins et al., 1996; Rickards et al., 1994; Savio et al., 2001), 55 to 90% at 1 kHz (Cone-Wesson et al., 2002; John et al., 2004; Lins et al., 1996; Savio et al., 2001), 50 to 100% at 2 kHz (Cone-Wesson et al., 2002; John et al., 2004; Lins et al., 1996; Savio et al., 2001), and responses were evoked by approximately 60 to 100% of newborns at 4 kHz (Cone-Wesson et al., 2002; John et al., 2004; Lins et al., 1996; Rickards et al., 1994; Savio et al., 2001). Inter-study differences in stimulus and recording parameters in the above-mentioned studies make comparisons of reported outcomes difficult to fully interpret. However, results of earlier research on the effects of aging, such as that of Aoyagi et al., (1994) and Maurizi et al. (1990) suggest that stability and detectability of ASSRs increase with increasing age.

In summary, a pronounced age affect appears to exist for all the AEPs. Studies of age-related changes in response amplitude and latency have demonstrated that generators of the ABR (and presumably the 80-Hz ASSR) reach maturity by 18 months to two years of age; the MLR (and presumably the 40-Hz ASSR) reaches maturity in early childhood, while the generators of the LLR reach maturity by adolescence (cf. Table 23).

This chapter subsection addressed the development of AEPs and discussed age-related changes that occur in response amplitude and latency as each of the evoked potential components underwent development. Subsection 3.5 will address stimulus factors that affect AEPs evoked by transient and steady-state stimuli.

Table 23 Summary of the Development of Auditory Evoked Potentials

Epoch (AEP)	Generators	Infant Response	Age of Maturation	Adult Response
AEPs Evoked by Transient Stimuli				
3-10 (ABR)	Distal part of the auditory nerve up through the LL.	Three primary vertex-positive peaks (I, III and V).	The waveform morphology of the infant response is similar to that of an adult between three to six months of age. Adult latency is reached by 18 months to two years of age.	A full complement of five to seven vertex-positive peaks (I-VII).
10-50 (MLR)	Cortical and subcortical generators of both primary and nonprimary auditory pathways.	Very broad-based waveform; the vertex-positive P_a being more prominent than its preceding negative wave N_a.	The waveform morphology and amplitude of the infant response is similar to that of an adult just after the first decade of life.	A waveform consisting of a N_a, P_a and N_b
50-250 (LLR)	The primary and secondary auditory cortex (midline and lateral temporal surface, respectively).	The vertex-positive wave P_2 followed by the intervening negative trough N_2.	The waveform morphology of the infant response is similar to that of an adult between three to six months of age. Adult latency and amplitude is reached just before the second decade of life.	A waveform consisting of P_1, N_1, P_2, and N_2.
AEPs Evoked by Steady-State Stimuli				
ASSR	Brainstem and tangential and radial cortical sources.	Amplitudes of 80-Hz ASSRs are typically 30 to 50% of an adult's response.	It is unclear what age the infant ASSR becomes similar to that of an adult. However, it is thought that the optimal modulation frequency changes from 80 Hz to 40 Hz at 13 years of age.	Stable responses with amplitudes comparable to those of an adult.

3.5 STIMULUS FACTORS THAT AFFECT AEPS

The relative characteristics of transient and steady-state stimuli are sensitive to recording the functional capabilities of the auditory system when electrophysiological tests of the brainstem and central auditory pathway are employed. This chapter subsection addresses the effects of these characteristics on response amplitude and latency (or phase) when recording AEPs evoked by transient and steady-state stimuli.

3.5.1 Transient Stimuli

Three types of transient stimuli are described classically: acoustic clicks, tone bursts (TBs) and tone pips. These stimuli do not regularly repeat in a given period of time (e.g., response analysis window in digital processing) and therefore are inherently aperiodic. Acoustic clicks are generated by rectangular pulses of direct current (DC; current that only flows in one direction), whereas TBs and tone pips are produced by pulses of alternating current (AC; current that periodically reverses direction). These transduced signals will have energy spread over a more or less broad spectrum; their energy will not be uniform across frequencies. Because the relative characteristics of transient stimuli--stimulus duration, rise and fall time, repetition rate and interstimulus interval (ISI), and polarity--are sensitive to recording the functional capabilities of the auditory system, this chapter subsection addresses the effects of these transient characteristics on AEP response amplitude and latency.

3.5.1.1 ABR

Stimulus duration

A study was undertaken by Hecox and Burkard (1982), in which the effect of stimulus duration on ABR latency was investigated. Results revealed that increasing the ABR stimulus on-time slightly prolonged the response latency for wave V in newborns. However, the newborns' prolonged response disappeared once a critical value of signal off-time was reached. These results are in sharp contrast to the effects of stimulus duration on ABR latency in adults.

Moore (1983), Beattie and Boyd (1984), and Gorga, Beauchaine, Reiland, Worthington, and Javel (1984) conducted comprehensive studies on the effects of manipulating stimulus duration. These investigators agree that stimulus duration does not have a marked influence on ABR latency and thresholds in adults. Moore investigated the effects of 4 kHz TBs with a rise and fall time of 1 msec presented at a constant rate of 9.2 per sec. Results revealed that the latency of ABR waves I and V increased slightly as duration increased from 3 to 100 msec. Although Beattie and Boyd (1984) utilized clicks presented at a constant rate of 10.1 per sec, latency data did not reveal significant changes when stimulus duration was manipulated using electrical pulses of 0.25, 0.5, 1, 2 and 4 msec. Similarly, in a related study Gorga et al. (1984) investigated 2 kHz TBs with a rise and fall time of 0.5 msec presented at rates between 2 and 4 msec. Results revealed that ABR thresholds were independent of stimulus duration that ranged from 1 to 256 msec and at 512 msec. These findings corresponded to previous data reported by Hecox, Squires, and Galambos (1976). Latency changes that might occur are thought to be a function of response recovery, adaptation or fatigue (Funasaka & Ito, 1986; Hecox et al., 1976).

Rise and fall time

The effects of stimulus rise and fall time on ABR latency have been examined in several studies. A study conducted by Hecox & Burkard (1982) revealed that increasing rise time of the stimulus increased the latency of the response to a greater extent in newborns compared to adults. However, the magnitude of this effect on latency for each ABR wave component was thought to have decreased somewhat with age (Hecox & Burkard, 1982). Likewise, results of earlier research involving adults revealed that increasing the rise time of the stimulus increased the latency of the response to ABR wave V (Cobb, Skinner, & Burns, 1978; Hecox et al., 1976; Kodera, Hink, Yamada, & Suzuki, 1979; Kodera, Yamane, Yamada, & Suzuki, 1977). To determine what part of the rise of the stimulus (i.e., early or late) is most effective in evoking a response, Suzuki and Horiuchi (1981) created two different recording paradigms using a series of tone pips with various rise times with the same slope. Tone pips at 0.5 and 2 kHz were presented at a rate of 13.3 per sec. Rise and fall times for 0.5 kHz were 1, 2, 3, 4, 6 and 10 msec, and for 2 kHz were 0.5, 1, 1.5, 2, 3 and 5 msec using a linear-shaped stimulus envelope. Results revealed the very early part of the stimulus was most effective in evoking a response. Responses at 0.5 kHz were evoked within 3 msec of the stimulus, whereas responses at 2 kHz were evoked within 1.5 msec of the stimulus. The prolongation of the rise time beyond the initial response yielded little improvement in the detectability of a response at either frequency. Effective rise times for 1 and 4 kHz were extrapolated from the data at 0.5 and 2 kHz. It was estimated that responses at 1 kHz would be evoked within 2 msec of the stimulus and responses at 4 kHz would be evoked within 1 msec of the stimulus.

Repetition rate and Interstimulus interval

Investigators agree that the more immature the auditory system, the greater the repetition rate variously affects the latency, the replicability, and the ease with which all the individual components of the response can be identified (Despland & Galambos, 1982; Fujikawa & Weber, 1977; Maurizi et al., 1986; Morgan et al., 1987; Salamy et al., 1975; Salamy et al., 1978; Starr et al., 1977; Stockard et al., 1979; Stockard, Stockard, & Coen, 1983). Numerous studies have reported that repetition rate had a disparate effect on the developing ABR (cf. Table 24). The latency of ABR waves I and V increased with increasing repetition rate in premature and in term infants. These differential effects also resulted in an increased I-V interpeak interval (Despland & Galambos, 1980, 1982; Fujikawa & Weber, 1977; Lasky & Rupert, 1982; Morgan et al., 1987; Salamy et al., 1978; Stockard et al., 1983; Stockard et al., 1978; Stockard et al., 1979; Zimmerman et al. 1987).

Other studies, designed to explore the effect on the developing ABR to stimuli presented at different rates, have produced a wide range of results. Lasky (1984) studied repetition-rate effects on ABR amplitude and latency in preterm infants, term infants and adults. Stimuli were clicks presented at a rate of 10, 20, 40, 50, 66⅔ and 80 per sec. Latencies increased and amplitudes decreased as a function of repetition rate at all ages tested. In addition, latency-rate linear functions revealed that latency decreased with increasing age for all six repetition rates. The largest latency change occurred for wave V and to a lesser extent wave I and III. These differences in the rate effects between the waves decreased with increasing age. Pratt and Sohmer (1976) demonstrated that repetition rate had a cumulative effect on ABR latency in children four to 14 years of age. Stimuli were clicks presented at rates of 5, 10, 20, 40, and 80 per sec. No appreciable increase in latency was observed for wave I as click rate increased.

However, latencies of later waves increased with increasing rate, with the effect being greatest on the later ABR waves.

Lina-Granade et al. (1993) conducted a comprehensive study to explore the effect of stimulus rate on ABR latency in infants ranging from 32 to 39 weeks conceptual age (CA). Stimuli were clicks presented at a rate of 20, 41.3 and 61.3 per sec. Latency-shifts between 20 per sec and 41.3 per sec (20-41.3), and between 20 per sec and 61.3 per sec (20-61.3) were calculated for all infants and compared with those of adults. No significant rate-induced latency shifts were found for Wave I. However, significant rate-induced latency shifts were shown for 20-41.3 and 20-61.3 for waves III and V, and for interpeak intervals III-V and I-V. Likewise, a study was undertaken by Jiang et al. (1998) in which the effects of stimulus rate of ABR latency was investigated in infants ranging from 37 to 41 weeks GA. Differences in wave latencies and interpeak intervals were compared to those of adults. Stimuli were clicks presented at a rate of 21, 51 and 91 per sec. Change rate (%) of ABR measures between the 21 per sec rate and the higher rates were calculated for all infants and compared to those of adults. All ABR wave latencies and interpeak intervals increased as click rate increased. No relationship was found between the latency of the interpeak interval of wave I-III and click rate. However, regression analysis did reveal a direct relationship between the latency of waves I, III and V, and the interpeak intervals of waves III-V and I-V, and click rate.

These results are in sharp contrast to the effects of stimulus rate on ABR latency in adults. Several investigators agree that relatively high stimulus rates in adults, between 11.1 and 70.0 per sec, have no appreciable effect on the ABR latency (Goldstein & Aldrich, 1999; Morgan et al., 1987; Salamy et al., 1975; Zimmerman et al., 1987) (cf. Table 24). However, Don, Allen and Starr (1977) reported that relatively high stimulus rates increased the latency of wave V by

approximately 0.5 msec when click rates increased from 10 to 100 per sec. Similarly, Weber and Fujikawa (1977) found that stimulus rates markedly influenced wave V latency when click rates increased from 13.3 to 67 per sec. In addition, to clarify the click rate effect on ABR wave latencies, Yagi & Kaga (1979) presented clicks with decreasing ISIs of 200, 100, 30, 20, 14 and 11 msec. No significant differences were found between the latencies of waves I, III and V at 200 msec and those at the 100 msec ISI condition. However, significant differences were found between latencies at 100 msec and those at 30, 20, 14 and 11 msec ISI conditions. In addition, latencies of later waves increased with increasing rate, with the effect being greatest on the later ABR waves. Moreover, van Olphen, Rodenburg, and Verwey (1979) found that stimulus rates of 10 Hz or less, did not affect the latencies of waves II through V. However, increasing the stimulus rate to 20, 40 or 80 Hz increased latencies of each of the above waves by the same magnitude, approximately 0.4 msec. Furthermore, Fowler & Noffsinger (1983) have reported that that relatively high stimulus rates increased the false positive rate in the identification of brainstem lesions.

In summary, because stimulus repetition rate affects the latency of ABR waves in infants and young children, the stimulus rate for assessment should be chosen by the type of information desired (i.e., hearing screening versus neurologic evaluation) (Stockard et al., 1978; Stockard & Westmoreland, 1981). However, as a general rule, the stimulus rate for an adult ABR assessment is typically around 20 per sec.

Table 24 Mean Latency Values of ABR Waves at Different Stimulus Repetition Rates

Study	Stimulus Rate	Stimulus Intensity	Term Wave I	Term Wave V	Adult Wave I	Adult Wave V
Jiang et al. (2004)	91.0	60 dB nHL	2.63 (0.21)	8.08 (0.29)		
Jiang et al. (1998)	91.0	60 dB nHL	2.69 (0.20)	8.11 (0.24)	2.37 (0.15)	6.71 (0.25)
Jiang et al. (2002)	91.0	60 dB nHL	2.70 (0.25)	8.14 (0.30)		
Jiang & Wilkinson (2008)	91.0	40 dB SL	2.63 (0.21)	8.08 (0.29)		
Lasky (1984)	80.0	70 dB SL	3.50 (0.70)	8.80 (0.60)	2.10 (0.40)	6.40 (0.30)
Chiappa et al. (1979)	70.0	60 dB SL			1.80 (0.21)	6.20 (0.30)
Galambos & Hecox (1978)	70.0	55 dB HL				6.25
Weber & Fujikawa (1977)	67.0	60 dB SL				6.18 (0.21)
Lasky (1984)	66.6	70 dB SL	3.40 (0.40)	8.50 (0.60)	1.90 (0.40)	6.20 (0.30)
Morgan et al. (1987)	66.6	75 dB nHL	2.13 (0.42)	7.74 (0.43)	1.82 (0.15)	6.00 (0.23)
Zimmerman et al. (1987)	66.6	75 dB nHL	2.11 (0.36)	7.72 (0.43)	1.82 (0.15)	6.00 (0.23)
Lina-Granade et al. (1993)	61.3	80 dB HL	2.21 (0.53)	7.36 (0.53)	1.84 (0.13)	5.98 (0.24)
Jiang et al. (2004)	51.0	60 dB nHL	2.46 (0.19)	7.62 (0.22)		
Jiang et al. (1998)	51.0	60 dB nHL	2.53 (0.20)	7.65 (0.18)	2.36 (0.18)	6.45 (0.20)
Jiang et al. (2002)	51.0	60 dB nHL	2.53 (0.22)	7.69 (0.29)		
Jiang & Wilkinson (2008)	51.0	40 dB SL	2.47 (0.19)	7.62 (0.22)		

Table 24 continued.

Lasky (1984)	50.0	70 dB SL	3.40 (0.90)	8.40 (0.50)	2.00 (0.40)	6.10 (0.30)
Lina-Granade et al. (1993)	41.3	80 dB HL	2.08 (0.52)	7.19 (0.49)	1.80 (0.15)	5.86 (0.21)
Lasky (1984)	40.0	70 dB SL	3.10 (0.60)	8.30 (0.50)	1.80 (0.50)	6.00 (0.30)
Salamy et al. (1978)	40.0	55 dB SL	2.23 (0.32)	7.65 (0.31)	1.58 (0.16)	5.70 (0.27)
Despland & Galambos (1982)	37.0	60 dB HL		7.62 (0.36)		
Galambos & Hecox (1978)	37.0	60 dB nHL		7.60		
Morgan et al. (1987)	33.3	75 dB nHL	2.12 (0.41)	7.26 (0.40)	1.76 (0.14)	5.75 (0.23)
Schulman-Galambos & Galambos (1975)	33.3	60 dB nHL		7.30		
Zimmerman et al. (1987)	33.3	75 dB nHL	2.11 (0.41)	7.24 (0.47)	1.76 (0.14)	5.75 (0.23)
Cox et al. (1981)	33.0	60 dB nHL	2.95 (0.20)	7.65 (0.19)	1.91 (0.23)	5.86 (0.27)
Weber & Fujikawa (1977)	33.0	60 dB SL				5.90 (0.22)
Yagi & Kaga (1979) [a]	33.0	70 dB HL				5.80
Kulekci, Terlemez, Ciprut & Akdas (2007)	31.0	70 dB nHL		6.79 (0.29)		5.50 (0.05)
Kulekci et al. (2007)	31.0	55 dB nHL		7.13 (0.34)		5.82 (0.25)
Chiappa et al. (1979)	30.0	60 dB SL			1.90 (0.26)	5.90 (.034)
Salamy et al. (1978)	30.0	55 dB SL	2.16 (0.37)	7.58 (0.33)	1.58 (0.15)	5.58 (0.20)
Eldredge & Salamy (1996)	23.0	60 dB nHL	1.45 (0.27)	6.40 (0.33)		

Table 24 continued.

Lima et al. (2008)	21.2	80 dB nHL			1.68 (0.12)	5.56 (0.26)
Jiang et al. (2004)	21.0	60 dB nHL	2.28 (0.18)	7.19 (0.20)		
Jiang et al. (1998)	21.0	60 dB nHL	2.33 (0.17)	7.24 (0.23)	2.13 (0.12)	6.14 (0.13)
Jiang et al. (2002)	21.0	60 dB nHL	2.33 (0.21)	7.22 (0.23)		
Jiang & Wilkinson (2008)	21.0	40 dB SL	2.29 (0.18)	7.20 (0.20)		
Lasky (1984)	20.0	70 dB SL	3.10 (0.50)	7.90 (0.50)	1.70 (0.30)	5.80 (0.20)
Lina-Granade et al. (1993)	20.0	80 dB HL	2.13 (0.58)	6.96 (0.45)	1.72 (0.11)	5.70 (0.18)
Eggermont & Salamy (1988)	15.0	55 dB SL	2.00 (0.31)	7.14 (0.43)	1.70 (0.16)	5.66 (0.23)
McPherson et al. (1989)	15.0	40 dB SL		7.50 (0.40)		6.10 (0.30)
Salamy & McKean (1976) [b]	15.0	55 dB SL	2.12 (0.35)	7.06 (0.38)	1.57 (0.14)	5.55 (0.26)
Salamy et al. (1982)	15.0	60 dB nHL	2.07 (0.36)	7.16 (0.44)	1.29 (0.15)	5.66 (0.23)
Weber & Fujikawa (1977)	13.3	60 dB SL				5.84 (0.30)
Mochizuki et al. (1982) [c]	13.0	85 dB SL	1.58 (0.15)	6.76 (0.25)	1.37 (0.06)	5.51 (0.21)
Morgan et al. (1987) [d]	11.1	75 dB nHL	2.03 (0.39)	6.91 (0.39)	1.71 (0.14)	5.54 (0.22)
Zimmerman et al. (1987)	11.1	75 dB nHL	2.05 (0.35)	6.87 (0.40)	1.71 (0.14)	5.54 (0.22)
Pasman et al. (1996)	11.0	70 dB SPL	2.56 (0.41)	7.53 (0.41)		
Pasman et al. (1992)	11.0	70 dB SPL	2.56 (0.50)	7.51 (0.43)		

Table 24 continued.

Rotteveel, Colon et al. (1986)	11.0	70 dB HL	2.58 (0.48)	7.53 (0.43)		
Rotteveel, de Graaf et al. (1987)	11.0	70 dB HL	2.74 (0.38)	7.65 (0.42)		
Beiser et al. (1985)	10.0	85 dB nHL	1.55 (0.13)	6.67 (0.29)	1.38 (0.06)	5.54 (0.15)
Chiappa et al. (1979)	10.0	60 dB SL			1.70 (0.15)	5.70 (0.25)
Despland & Galambos (1980) [e, f]	10.0	60 dB HL		7.35 (0.46)		5.60
Despland & Galambos (1982)	10.0	60 dB HL	2.28 (0.27)	7.35 (0.46)		
Fawer & Dubowitz (1982)	10.0	60 dB HL	2.42 (0.32)	7.29 (0.37)		
Goldstein et al. (1979)	8.0-12.0	65 dB SL	1.64 (0.18)	6.74 (0.22)	1.53 (0.14)	5.56 (0.20)
Jiang et al. (1991)	10.0	70 dB HL	1.94 (0.17)	6.84 (0.23)	1.71 (0.11)	5.64 (0.18)
Krumholz et al. (1985)	10.0	65 dB nHL	1.86 (0.18)	6.80 (0.28)	1.68 (0.12)	5.67 (0.21)
Lasky (1984)	10.0	70 dB SL	3.00 (0.60)	7.60 (0.50)	1.60 (0.30)	5.70 (0.40)
Salamy et al. (1978)	10.0	55 dB SL	2.12 (0.36)	7.11 (0.28)	1.51 (0.08)	5.39 (0.24)
Starr et al. (1977) [g]	10.0	65 dB SL	1.80	6.90	1.60	5.70
Stockard et al. (1983)	10.0	≤110 dB peSPL	1.81 (0.22)	6.72 (0.32)		
Stockard et al. (1978)	10.0	60 dB SL				5.85
Stockard et al. (1979)	10.0	70 dB HL (SL in adults)	1.81 (0.22)	6.72 (0.32)	1.62 (0.12)	5.62 (0.23)

Table 24 continued.

Note: Comparative survey of mean latency values of ABR waves at different stimulus repetition rates in term infants and adults. Mean latency values are in msec; SDs (in parentheses). Click stimuli were used in all the above studies. Stimulus rate is per sec. Term infant is defined as 37-42 weeks GA. Adults were typically defined by investigators as > 15 years of age. In some studies absolute latencies for children and adults were grouped together (ranging from 5-33 years of age). In these cases ([b, c] and [d]), mean latency and SD values were defined in the Table above as adult. Discrepancies across studies may be due to variations in equipment, methods and recording conditions.

[a] Estimated response latency value from Figure 2.

[e] Mean and SD latency values published in Rotteveel, Colon et al. (1986).

[f] Estimated response latency value from Figure 4.

[g] Mean latency values published in Starr &Amlie (1981).

Polarity

The effects of click polarity (initial direction of signal voltage) on ABR latency have been examined in several studies. Results from these studies have revealed differences in ABR latencies between rarefaction (R) and condensation (C) clicks, particularly in newborns and young children. In general, peak latencies are always shorter in response to R compared to C clicks (Lima et al., 2008; Ornitz, Mo, Olson, & Walter, 1980; Ornitz & Walter, 1975; Stockard et al., 1983; Stockard et al., 1979; Stockard & Westmoreland, 1981), and are more enhanced in newborns compared to adults (Ornitz & Walter, 1975). Although the effects of stimulus polarity tended to be somewhat variable, the most consistent polarity-related ABR finding was the influence to both wave I and the I-V interpeak interval in newborns and young children (Salt & Thornton, 1984; Stockard et al., 1983; Stockard et al., 1979 Stockard & Westmoreland, 1981; Schwartz et al., 1989) (cf. Table 25). Some studies have shown an opposite polarity pattern, that is, shorter peak latencies in response to C compared to R clicks (Schwartz et al., 1989; Stockard et al., 1978; Stockard et al., 1979); others have reported no differential response to R and C clicks (Ornitz & Walter, 1975; Stockard et al., 1979); while still others have reported significant C-R latency differences involving different ABR wave components (Ornitz et al., 1980; Ornitz & Walter, 1975; Stockard et al., 1978). Despite the fact the above studies have indicated that polarity influences ABR latency in newborns and young children, no systematic investigation has been employed which support polarity preference.

Very few studies have investigated the effects of click polarity on ABR amplitudes. A study undertaken by Schwartz et al. (1989) revealed significant differences in wave I amplitudes between click polarities in infants; R stimuli provided greater amplitude compared to C. In addition, the amplitude of wave I in infants and adults were essentially the same for C and for R

polarities. Moreover, wave V amplitudes in infants were almost one-half (≅0.28 μV) that of an adult across both click polarities (≅0.60 μV for C and 0.70 μV for R).

In summary, several outcomes have been determined from the corresponding research concerning stimulus factors that affect the ABR. In infants and young children, ABR stimulus on-time and rise and fall time have been found to increase the latency of the response. In addition, results of past studies have suggested a direct relationship between maturity along the CAP and the effect of rate on the ABR. Increasing the stimulus repetition rate--which primarily acts to increase stress on the auditory system--has a pronounced influence on ABR latency and morphology in newborns. Thus, stimulus rate for infant ABR assessment should be chosen by the type of information desired (i.e., hearing screening versus neurologic evaluation). Furthermore, click polarity has a disparate effect of the developing ABR, such that, differences in latency between click polarities most often influence both wave I and the I-V interpeak interval in newborns and young children. Conversely, in the adult, stimulus duration, repetition rate and polarity have no appreciable effect on the ABR latency. In addition, latency of the response seems to be determined by the very early part of the stimulus--3 msec at 0.5 kHz and 1.5 msec at 2 kHz--and the succeeding part yields little improvement in the detectability of a response.

Table 25 Mean Latency and Amplitude Values at ABR Waves at Different Polarities

Latency and Interpeak Values				
Study	**Term I**	**Term I-V**	**Adult I**	**Adult I-V**
Condensation				
Lima et al. (2008)			1.71 (0.12)	3.98 (0.19)
Rotteveel, Colon et al. (1986)	2.58 (0.48)	4.95 (0.24)		
Rotteveel, de Graaf et al. (1987)	2.74 (0.38)	4.91 (0.31)		
Scherg & Speulda (1982)			1.89 (0.16)	4.00 (0.22)
Stockard et al. (1979)	1.94 (0.25)	4.79 (0.30)	1.69 (0.19)	3.95 (0.26)
Rarefaction				
Lima et al. (2008)			1.68 (0.12)	3.87 (0.26)
Jiang et al. (2004)	2.28 (0.18)	4.96 (0.17)		
Jiang et al. (1998)	2.33 (0.17)	4.96 (0.20)	2.13 (0.12)	4.01 (0.15)
Jiang et al. (2002)	2.33 (0.21)	4.90 (0.17)		
Jiang & Wilkinson (2008)	2.29 (0.18)	4.93 (0.20)		
Jiang et al. (1991)	1.94 (0.17)	4.89 (0.24)	1.71 (0.11)	3.94 (0.18)
Krumholz et al. (1985)	1.86 (0.18)	4.92 (0.29)	1.68 (0.12)	3.99 (0.20)
Lima et al. (2008)				
Morgan et al. (1987) [a]	2.03 (0.39)	4.80 (0.39)	1.71 (0.14)	3.83 (0.24)
Pasman et al. (1996)	2.56 (0.41)	4.98 (0.29)		

Table 25 continued.

Pasman et al. (1992)	2.56 (0.50)	4.95 (0.25)		
Scherg & Speulda (1982)			1.82 (0.16)	4.05 (0.21)
Stockard et al. (1983)	1.81 (0.22)	4.90 (0.28)		
Stockard et al. (1978)				4.00
Stockard et al. (1979)	1.81 (0.22)	4.92 (0.26)	1.62 (0.12)	4.02 (0.24)
Zimmerman et al. (1987)	2.05 (0.35)	4.82	1.71 (0.14)	3.83
Amplitude and Ratio Values				
Study	**Term Wave 1**	**Term V-I**	**Adult Wave I**	**Adult V-I**
Condensation				
Rotteveel, Colon et al. (1986)		1.09		
Rotteveel, de Graaf et al. (1987)	0.18 (0.07)	1.10 (0.50)		
Schwartz et al. (1989) [b, c]	0.36	.63	0.36	1.46
Rarefaction				
Jiang et al. (2004)				
Jiang et al. (1998)	0.15 (0.05)	1.58 (0.73)	0.11 (0.05)	3.29 (1.34)
Jiang et al. (2002)				
Jiang & Wilkinson (2008)	0.17 (0.06)	1.46 (0.93)		
Pasman et al. (1996)	0.17 (0.05)	1.46 (0.93)		

Table 25 continued.

Pasman et al. (1992)	0.20 (0.04)	1.03 (0.34)		
Schwartz et al. (1989) [b, c]	0.46	.77[c]	0.48	1.86

Note: Comparative survey of mean latency and amplitude values of ABR waves at different polarities in term infants and adults. Mean latency and interpeak values are in msec and mean amplitude and ratio values are in μV and; SDs (in parentheses). Stimuli were presented between 10 and 21.2 clicks per sec. in most of above studies. The exception is Schwartz et al. (1989), in which no stimulus repetition rate was published. Term infant is defined as 37-43 weeks GA. Adults were typically defined by investigators as > 18 years of age. In one study ([a]) absolute latencies for children and adults were grouped together (ranging from 9-29 years of age). In this case, mean latency and SD values were defined in the Table above as adult. Discrepancies across studies may be due to variations in equipment, methods and recording conditions.

[b] Absolute amplitude values were estimated from Figure 2.

[c] Amplitude ratios were calculated from values that were estimated from Figure 2.

3.5.1.2 MLR

Stimulus duration

A study was undertaken by Skinner and Antinoro (1971), in which the effects of stimulus duration at two different rise times were evaluated in adults. Tone bursts at 1 kHz with a rise time of 0.1 msec were presented at durations of 0.2, 0.4, 10, 20, 30, 40 and 50 msec, and with a rise time of 0.5 msec were presented at durations of 1, 5, 10, 20 and 40 msec. Amplitude results revealed no clear trend when the rise time or the duration of the TBs was manipulated. Thus, like the ABR, the MLR is thought to be primarily an onset response.

Rise and fall time

Investigators agree that MLR amplitude decreased as rise time increased in adults (Beiter & Hogan, 1973; Kodera et al., 1979; Kodera et al., 1977; Lane, Kupperman, & Goldstein, 1971; Skinner & Antinoro, 1971; Vivion, Hirsch, Frye-Osier, & Goldstein, 1980; Xu, De Vel, Vinck, & van Cauwenberge, 1997). Results were found to be greater for the later (i.e., $P_a - N_b$) than for the earlier MLR wave components (i.e., $N_a - P_a$) (Beiter & Hogan). To provide additional information regarding the effect of stimulus rise and fall time on MLR amplitude, Beiter & Hogan (1973) investigated the extent to which the rise time of a 1 kHz tone could be increased and without reducing the amplitude of the middle component responses. Results of studies have suggested that stimulus rise time could be increased to 5 msec without sacrificing the effectiveness to evoke a cortical response. These results are in good agreement with data reported by Vivion et al. (1980), who assert that stimulus equivalent duration of less than 10 msec are optimal for eliciting identifiable middle component responses. Likewise, Xu et al. (1997) recommended that a rise and fall time of 4 msec be used to elicit the MLR. An envelope time of 4-2-4 was found to maintain not only the frequency specificity of the stimulus at 0.5, 1,

and 2 kHz, but was also found to maintain the synchronization of neural firings necessary to obtain an MLR.

Repetition rate and Interstimulus interval

Investigators agree that the more immature the auditory system, the greater the repetition rate variously affects the amplitude on the developing MLR. Fifer (1985) conducted a comprehensive study to determine the optimum stimulation rate for premature neonates and infants ranging from 28 to 44 weeks CA. Stimuli were tone pips presented at a rate of 1.1 and 2.1 per sec, and from 5.1 to 40.1 per sec. Amplitude results revealed that developing MLR components evoked by tone pips at 0.5 kHz were best observed at presentation rates of 1 or 2 per sec, and were rarely observed at presentation rates greater than 5 per sec. Similarly, Jerger, Chmiel, Glaze, and Frost (1987) revealed that developing MLR components evoked by TBs at 0.5 kHz were best observed at presentation rates as slow as 1 to 2.5 per sec, and were rarely observed at presentation rates as fast as 4 to 10 per sec in sleeping infants two to six months of age.

However, according to Tucker and Ruth (1996) signal rates as low as 3.3 per sec did not have a significant effect on MLR measurements in infants who remained awake during assessment. Likewise, Tucker and Ruth, and McFarland, Vivion, Wolf and Goldstein (1975) agree that repetition rate had little or no consistent effect on the amplitude of selected mature response components of the MLR in adults. However, the use of presentation rates higher than about 15 per sec decreases the amplitude of the MLR, until the repetition rate approaches 40 per sec in adults (cf. auditory steady-state response). Thus to avoid degradation of the response in the mature and developing MLR, it is recommended that stimuli be presented at rates of 5 to 11

per sec for adults, and as low as 2 to 3 per sec for infants and young children (Geisler et al., 1958; McPherson & Ballachanda, 2000; Thornton, Mendel, & Anderson, 1977).

In summary, several outcomes have been determined from the corresponding research concerning stimulus factors that affect the MLR. In infants and young children, increasing the repetition rate--which may not allow complete repolarization of the neuron--has a pronounced influence on MLR amplitude and morphology for newborns. Thus, to avoid degradation of the response in the developing MLR, it is recommended that stimuli be presented at rates as low as 2 to 3 per sec for infants and young children. In adults, MLR amplitude results revealed no clear trend when the rise time or the duration of the stimulus was manipulated. Thus, like the ABR, the MLR is thought to be primarily an onset response. Investigators agree that MLR amplitude decreases as rise time increases in adults. However, it was found that the rise time of a 1 kHz tone could be increased to 5 msec without sacrificing the effectiveness to evoke a cortical response. In addition, the amplitude of the response seems to be best evoked when stimuli is presented at rates of 5 to 11 per sec for adults.

3.5.1.3 LLR

Stimulus duration

A study was undertaken by Davis and Zerlin (1966) in which the effects of stimulus duration on LLR amplitude and latency were investigated. Tone bursts at 1.2 kHz with a rise and fall time of 5 msec were presented with plateau durations that varied from 2 to 320 msec. Results revealed no systematic increase in N_1P_1 amplitude as TB duration was increased. Comparable results were reported by Skinner and Jones (1968) when TBs at 1 kHz with a rise time of 0.1 msec were presented at durations of 10, 25, 50, 75, 100 and 150 msec. The authors concluded that varying TB duration had little or no consistent effect on the amplitude of selected response components

of the LLR. Thus, even for very brief plateau durations these investigators agree that LLR amplitude is quite independent of stimulus duration.

Other authors, however, have concluded differently. Onishi and Davis (1968) studied the effects of TB duration using two different rise times, 3 and 30 msec, and six different durations of plateau. Tone bursts at 1 kHz were presented at plateau durations of 0, 3, 10, 30, 100 and 300 msec. Tone bursts with a rise time of 3 msec showed marked effects of stimulus duration on the amplitude and latency of the response. Results revealed that N_1P_2 amplitude and the latency of N_1 increased as the duration of the stimulus plateau increased from 0 to 30 msec. However, when the duration of the stimulus plateau was increased beyond 30 msec both the amplitude and latency of the response remained constant. These findings confirmed earlier results obtained by McCandless and Best (1966) who assert there were no consistent differences in N_1P_2 amplitude between pure tones at 1 kHz with plateau durations greater than 30 msec. Comparable results were also reported by Cody and Klass (1968). These authors concluded that changing the duration of the stimulus from 30 to 200 msec had no significant influence on the accuracy of 1 kHz LLR threshold responses.

Results of later research on stimulus duration reported somewhat discrepant findings. Alain, Woods and Covarrubias (1997) studied the effects of stimulus duration using three different durations. Tone bursts of 0.25, 1, and 4 kHz were presented at durations of 8, 24 and 72 msec. Results demonstrated that changes in stimulus duration increased the amplitudes of N_1 and P_2 deflections. This trend was evident across all stimulus frequencies. Likewise, according to Nelson, Hall and Jacobson (1997) N_1P_2 amplitudes increased when stimulus duration was increased from 5 to 60 msec for 0.5 and 4 kHz TBs. Similarly, Müller (1973) studied the effects of stimulus duration, in which TBs at 1 kHz with a rise time of 2 msec were presented at

durations of 5, 20, 50, 100 and 250 msec. No consistent differences were noted in the N_1P_2 amplitude when the stimulus plateau ranged from 20 to 50 msec. However, when durations were greater than 50 to 75 msec there were striking changes in the amplitude and latency of the response, which were possibly due to interactions between tone onset and offset (Davis, 1976; Keidel, 1976; Rose & Malone, 1965; Spreng, 1969). Thus, these investigators and others (McPherson & Ballachanda, 2000) agree that an effective stimulus plateau should fall between 25 and 50 msec.

Rise and fall time

A small group of studies have reported the effects of stimulus rise and fall time on LLR amplitude and latency in adults; however, outcomes reported were variable. A study was undertaken by Skinner and Jones (1968), in which the effects of stimulus rise time were examined to determine possible effects on the amplitude and latency of various components of the LLR. Tone bursts of 1 kHz with 75 msec duration were presented at rise times of .10, 5, 10, 25 and 50 msec. Results demonstrated that changes in the rise time of the stimulus increased the P_1N_2 amplitude, but had no affect on P_1 and N_2 latency. In comparison, Davis and Zerlin (1966) used TBs of 1.2 kHz with 5 msec duration presented at rise times of 2.5, 5, 10, 25, 50 or 100 msec. No clear trends related to the rise time of the stimulus were observed for N_1P_2 amplitude, suggesting that response amplitude is independent of duration. Likewise, no clear trends were observed in the latency characteristics of the LLR.

To extend the observation of Davis and Zerlin, Onishi and Davis (1968) further evaluated the effects of stimulus rise time using TBs of 1 kHz with 2.5 msec duration presented at rise times of 3, 10, 30, 50, 100 and 300 msec. Results revealed that N_1P_2 amplitude gradually decreased as rise time increased beyond approximately 30 msec. In addition, results

demonstrated that the latency of N_1 increased as rise time increased. In a related study, Ruhm and Jansen (1969) explored the effects of stimulus rise time via extrapolated threshold measures. Tone bursts of 3 kHz were presented randomly at rise times that ranged from 10 to 1,000 msec. Results demonstrated that N_1P_2 amplitude steadily decreased as rise time increased from 10 to 1,000 msec, whereas N_1 latency increased as rise time increased from 10 and 50 msec. Likewise, Kodera et al. (1979) averaged responses to 1 kHz TBs with 42 msec duration presented at rise times of 5, 10 or 20 msec. Amplitude results revealed that N_1P_2 amplitude decreased and N_1 and P_2 latency increased as rise times increased. Differences in the above-mentioned investigations might be brought about by differences in signal generation and measurement techniques, interactions between the LLRs to tone onset and offset, or both. Although it is difficult to draw a cohesive picture from the aggregate of information, the most consistent finding was that longer rise times were associated with longer latencies and smaller amplitudes. Thus, to obtain a recordable LLR, Davis (1976) and McPherson (1996) recommend that the rise time be less than 20 msec.

Repetition rate and Interstimulus interval

Only a few studies have reported the influence of stimulus repetition rate on LLR amplitude and latency. Rapin (1964) studied slow rates of stimulation and irregular spacing of stimuli in infants and young children. Clicks were presented at regular rates of 1 per 3 sec and irregular rates averaging 1 per 3sec. Rapin reported the most effective stimulus rate lies between 1 per 3sec and slower than 1 per sec. Likewise, Nelson et al. (1997) examined the influence of stimulus rate on P_b amplitude, in which TBs at 0.5 kHz, 4 kHz, and clicks were presented at 0.5, 1.1, 2.1 and 5.1 per sec in children and adults. Results demonstrated that as stimulus rate increased detectability of the P_b component decreased for all three stimulus types. Results demonstrated that the P_b

component of the LLR was best evoked by very slow repetition rates of 0.5 and 1.1 per sec. Likewise, McCandless and Best (1964) examined the effects of different stimulus rates on the amplitude and latency of the N_1P_2 response in adults. Clicks were presented at stimulus rates of 3 per sec, 2 per sec, 1 per sec and 0.5 per sec, and randomly at rates ranging from 0.25 per sec to 0.16 per sec. Amplitude results revealed that stimulus rates of 2 per sec or faster decreased the N_1P_2 response, while stimulus rates slower than 0.5 per sec had little effect on the N_1P_2 response. Durrant (1987b) reported results somewhat at variance with the above-mentioned study. Durrant examined the effects of stimulus rate on response amplitude using a 'pattern-reversal stimulus' (i.e., alternating frequency modulated tone complex). The stimulus was presented at reversal rates ranging from 0.4 to 1.6 per sec. The P_1-N_1-P_2 complex of the LLR was found to be robust, even at rates as slow as 0.4 per sec. However, the amplitude of the response was found to decrease with increasing reversal rate.

To determine the relation of the amplitude of the response to the interval between stimuli, Davis, Mast, Yoshie, and Zerlin (1966) conducted a comprehensive study in which tone pips of 2.4 kHz were presented at fixed ISIs between 0.5 and 6 sec in adults. Results revealed that N_1P_2 amplitude increased with increasing ISI. The authors further suggested that the amplitude of the response could continue to increase with intervals of more than 10 sec. Comparable results were reported by Nelson and Lassman (1968) when intervals for pulsed pure tones of 0.5, 1, and 2 kHz were 0.25 through 10 sec. The authors concluded that N_1P_2 amplitude increased as a function of ISI, as well as speculated that this function would continue beyond intervals of 10 sec. Likewise, Milner (1969) presented pulsed 1 kHz tones at rates of 1.3 per sec, 1 per sec, 1 per 2 sec, 1 per 7 sec, and at 1 per 13.5 sec. Results revealed that N_1P_2 amplitude increased with

increasing ISI up to 8 sec. These findings were also confirmed later by Picton, Woods, Baribeau-Braun, and Healey (1977).

To extend these results, Davis et al. (1966) employed ISI paradigms using paired tone pips in which the short interval between pairs was 0.5 sec and the long interval, between pairs, was either constant at 3.0 sec, or was 2, 5, 7.5, 10, 15 and 20 sec. Results revealed that the N_1P_2 amplitude response to the second pair was one third the amplitude response of the first pair. Nelson, Lassman and Hoel (1969) studied the effects of fixed and variable-interval signal presentation schedules on the LLR. Tone bursts of 1 kHz were presented at either a fixed-interval of 2 sec or a variable-interval schedule ranging from 1 sec to 4.5 sec with an average interval of 2 sec. No significant advantage was found for a variable-interval versus a fixed-interval schedule with the same average interval of 2 sec. Comparable results were reported by Rothman, Davis and Hay (1970), in which 128 clicks were delivered either at regular intervals of 2.5 sec, irregular intervals of 2.5, 0.5, 2.5 and 4.5 sec, or delivered with no regularity. Although the amplitude for both fixed and variable presentations increased monotonically as a function of ISI, the amplitudes of the responses evoked by irregular stimulation were only slightly larger than those responses obtained from fixed stimulation.

In children, Paetau et al. (1995) recorded magnetoencephalographic (MEG) responses to pure tone and phonemic evoked LLRs. Tones of 1 kHz and pseudo-words (consonant-vowel syllables) were presented using different ISIs ranging from 0.9 to 2.4 sec. Under the shortest ISI condition (0.9 sec), children up to 12 years of age showed a biphasic N_1-P_1 response. Under longer ISIs (i.e., 1.2 to 2.4 sec) a separation of N_1 from the biphasic waveform appeared in all children. In addition, the latency of P_1, N_1 and N_2 decreased most rapidly in children <7 years of age. To extend these findings, Rojas et al. (1998) recorded MEG responses at longer ISIs in

children 6 to 18 years of age. Tone bursts of 1 kHz were presented using ISIs of 2, 4, 6, 8, 10 and 12 sec. In younger children, 6 to 8 years of age, N_1 amplitude linearly increased between all ISI conditions, whereas in older children, 15 to 17 years of age, N_1 amplitude increased when the ISI was increased from 2 to 4 sec, and then reached an asymptote when the ISI was increased to 6 sec. In addition, the latency of N_1 decreased as a function of age. These results were consistent with results from Paetau et al., who assert that the N_1 refractory period is longer in young children than in adults, and decreases with age.

Similarly, Ceponiené, Cheour, and Näätänen (1998) presented 1 kHz tones in separate blocks using constant ISIs (offset-to-onset) of 350, 700 and 1400 msec in children 7 to 9 years of age. Results show that in the shortest (350 msec) ISI condition, only P_1 and N_2 were observed, and at the longest (1400 msec) ISI condition N_1 was the most robust. In addition, the latency of P_1 and N_1 increased as the ISI was decreased from 1400 to 350 msec. Likewise, Ceponiené, Rinne and Näätänen (2002) presented partial harmonic tones with short (700 msec) and long (5 sec) stimulus onset asynchrony (SOA) in 4- and 9- year old children and adults. In children 4 years of age, the N_1 could not be obtained in any SOA condition. However, the N_1 in the 9 year old children could be detected in both the short-SOA--after the slow N_2 wave was filtered out--and in the long-SOA condition. Moreover, in the long-SOA condition, 9 year old children demonstrated larger amplitude and longer latency of the peak corresponding to the P_1 wave, whereas, adult's demonstrated larger amplitudes of the N_1 and P_2 waves and longer latencies of the P_1 and P_2 waves.

Other studies have also produced evidence that the amplitude and latency of LLR components change with increasing age and ISI condition. To examine the developmental change in the peaks of the N_1 and N_2 components, Takeshita et al. (2002) recorded MEG

responses to TB evoked LLRs. Tones of 1 kHz were presented using ISIs of 1.6, 3.0 and 5.0 sec in children 6 to 14 years of age and in adults. Results revealed that N_1 amplitude increased and latency decreased with increasing age and ISI condition. In contrast, N_2 amplitude decreased while the latency remained unchanged with increasing age and ISI condition. Likewise, Gilley et al. (2005) presented the /uh/ speech syllable at four presentations with decreasing ISIs of 2000, 1000, 560, and 360 msec in children 3 to 12 years of age and in adults. The peak corresponding to P_1 was clearly apparent in all age groups in all ISI conditions. In children 7 to 8 years of age, P_1 shows a small negative deflection (N_1) in the waveform, but when elicited only by an ISI of 2000 msec. By 11-12 years of age, children demonstrated discrete peaks of the P_1 and N_1-P_2 in all ISI conditions; however, the N_1-P_2 complex was most robust at 2000 msec. In adults, the N_1-P_2 complex was dominant in all ISI conditions. Moreover, the amplitude and detectability of the N_1-P_2 complex increased as a function of age and ISI condition.

Correspondingly, Sussman et al. (2008) presented 880 Hz pure tone using SOAs of 200, 400, 600 and 800 msec in children 8 to 16 years of age and adults. In the youngest age groups (8, 9, and 10 years) discrete peaks of P_1 and N_2 were observed in all SOA conditions, while P_2 could only be observed at the longest (800 msec) SOA condition. At 11 years of age, P_1 and N_2 can be seen at the shortest (200 msec) SOA condition, whereas P_2 can be seen as an invagination of the waveform at 400 msec and emerged as a discrete peak at 600 msec. Responses observed at 16 years of age are similar to those observed at age 11, however, N_2 can only be observed at 400 msec, and the N_1 component can now be seen in the 800 msec. In adults, the peak corresponding to P_1 was present at the shortest SOA condition, P_2 at 400 msec, and the N_1 component was clearly present at 400-800 msec. Moreover, the latency of P_1 decreased with

age, whereas P_2 and N_2 remained stable until 16 years of age. The amplitude of P_2 decreased with age, whereas N_2 remained stable until 16 years of age.

In summary, several outcomes have been determined from the corresponding research regarding stimulus factors that affect the LLR. Results from recent studies have suggested a relationship between maturity of the CAP and the effect of ISI on the LLR. In children, detectability of LLR components increases with age and ISI. In addition, for the elicitation of the N_1component, stimuli needs to be presented with an ISI of at least 1 sec due to the longer refractory period in children <11 years of age. In adults, it is recommended that the stimulus plateau fall between 25 and 50 msec in order to effectively evoke a cortical response. Although the information related to the effects of rise and fall time on the amplitude and latency of the LLR was quite variable, we can at least conclude that longer rise times are associated with longer latencies and smaller amplitudes. Thus, it is recommended that the rise time be less than 20 msec in order to obtain a recordable adult LLR. In addition, investigators agree to obtain maximal amplitude of the LLR the most effective stimulus rate is 2 per sec or less with an ISI greater than 6 sec for adults.

To recapitulate, stimulus parameters needed to obtain transient AEPs are as follows: (a) a rise time of less than 3 msec and a stimulus rate of 20 per sec or less to obtain a reproducible ABR in an adult (b) a rise time of less than 10 msec and a stimulus rate of 5 to 11 per sec to obtain a reproducible MLR in an adult, and a stimulus rate of 2 to 3 per sec to obtain an accurate MLR in a child, and (d) a stimulus plateau between 25 and 50 msec, a rise time of less than 20 msec, and a stimulus rate of less than 2 per sec with an ISI of at least 6 sec to obtain a reproducible LLR in an adult.

3.5.2 Steady-State Stimuli

Steady-state stimuli employed in evoked potential testing are complex tones. These stimuli regularly repeat themselves in a given time period and therefore are continuous in time. Unlike transients, steady-state stimuli will have energy concentrated at discrete frequencies. Waveform variations or modulations are used to vary their amplitude, frequency, or both. Because the relative characteristics of steady-state stimuli--stimulus intensity, modulation depth, phase, carrier frequency and modulation frequency--are sensitive to recording the functional capabilities of the auditory system, this chapter subsection addresses the effects of these characteristics on response amplitude and phase of ASSRs modulated at 40-Hz and 80-Hz. It should be noted that these effects, with the exception of only a few relative characteristics, most often have been documented in studies which involved adults.

3.5.2.1 ASSR

Stimulus Intensity

Investigators agree that 40-Hz amplitude and phase increased, or correspondingly, latency and phase delay decreased as a function of stimulus intensity (Galambos et al., 1981; John, Dimitrijevic, van Roon, & Picton, 2001; Klein 1983; Picton, Skinner et al., 1987; Rodriguez, Picton, Linden, Hamel, & Laframboise, 1986; Ross, Borgmann, & Draganova, 2000; Stapells et al., 1984; Szyfter, Dauman, & Charlet de Sauvage, 1984). In addition, amplitude increased consistently as a function of stimulus intensity when modulation frequencies as low as 4 Hz (Elliot, Green, & Lindsey, 1984; Rees 1982; Rees et al., 1986) and as high as 80 Hz (Kuwada et al., 1986; Lins et al., 1996; Savio et al., 2001) were used.

The potential usefulness of recording ASSRs to the same carrier frequency at different stimulus intensities was examined by Lins and Picton (1995) using two different paradigms. Lins and Picton examined the effects of stimulus intensity on 80-Hz ASSR amplitude using the same AM carrier frequency simultaneously presented to the same ear at two different intensities. Two AM carrier frequencies of 1 kHz modulated at 81 and 97 Hz were combined and simultaneously presented to the same ear. Carrier 1 was presented at a fixed intensity of 60 dB SPL, whereas carrier 2 was presented at intensities of 54, 60 and 66 dB SPL. Results revealed that the amplitude of the response to carrier 1 was significantly larger when presented alone than when it was presented with carrier 2 for all intensities. For example, when carrier 1 and carrier 2 were simultaneously presented at 60 dB SPL, the amplitude of the response for carrier 1 was reduced by 58%. Furthermore, there were additional responses resulting from the interactions between the two carriers, which appeared to represent distortion product responses ($2F_1+ F_2$ and $2F_1 – F_2$). To extend these results, Lins and Picton recorded responses at four different intensities. Four AM carrier frequencies of 1 kHz modulated at 105, 97, 87 and 81Hz with stimulus intensities of 70, 60, 50 and 40 dB SPL respectively, were presented either alone or simultaneously to the same ear. Results revealed that when carriers were presented alone the amplitudes of the responses were larger than when carriers with different intensities were simultaneously presented to the same ear. More notable, however, were the significant differences in amplitude between carriers presented alone versus carriers simultaneously presented at 60 dB SPL.

Results from several other investigations have also shown differences between responses obtained to stimuli individually and simultaneously presented to same ear or both ears at different stimulus intensities. Lins et al. (1995) examined 1 kHz AM tones modulated at a

frequency of 91 Hz presented monaurally at intensities that were varied from 20 to 90 dB SPL. Vector average measurements revealed that the slope of the amplitude function was significantly larger after 70 dB SPL than before 70 dB SPL. Using an ipsilateral high-pass masking noise significantly attenuated amplitude responses when stimulus intensities were 70 and 80 dB SPL, allowing only fibers with characteristic frequencies near 1 kHz to be activated. John, Lins, Boucher and Picton (1998) further evaluated effects of stimulus intensity on 80-Hz ASSR amplitude of using different AM carrier frequencies simultaneously presented to the same ear at high and low intensities. Tones of 1 and 2 kHz were presented alone and in combination with 0.5 kHz and 4 kHz to create two- and four-tone stimulus conditions. All carrier frequencies were separated by one octave and simultaneously presented to the same ear at intensities of 35 and 75 dB SPL. No significant differences were found in the amplitudes of the response when AM tones were presented alone or when they occurred in combination with other carrier frequencies at 35 dB SPL. However, when four carrier frequencies were simultaneously presented at 75 dB SPL, response amplitudes were significantly reduced from their original value (presented alone). John et al. concluded that greater interactions between stimuli occur at high stimulus intensities, such that high carrier frequencies attenuated the response to low carrier frequencies when stimulus intensity was increased to 75 dB SPL.

Likewise, Herdman and Stapells (2001) found similar results when the differences between various monaural and binaural stimulus conditions were investigated. Response amplitudes were elicited by AM tones modulated at frequencies between 77 and 105 Hz that were individually or simultaneously presented to the same ear or both ears at 30 and 60 dB SPL. Results revealed that 80-Hz ASSR amplitudes were not significantly different whether single or multiple AM tones were simultaneously presented to the same ear or both ears at 60 dB SPL or

less. Moreover, Picton et al. (2009) recorded responses to simultaneously presented multiple tones to the same ear at high and low intensities. Responses were recorded to AM tones at .5, 1, 2, and 4 kHz at intensities of 53 and 73 dB SPL. Modulation frequencies descended with increasing carrier frequency. At the 53 dB SPL intensity, multiple-stimulus responses produced an inverted U-shaped curve, such that amplitudes were highest at 1 and 2 kHz and lowest at .5 and 4 kHz, whereas an opposite response pattern was obtained at 73 dB SPL intensity--amplitudes were lowest at 1 and 2 kHz and highest at .5 and 4 kHz. Furthermore, the amplitude of a single-stimulus response to a 1 kHz tone presented at 53 dB SPL was similar to the 1 kHz multiple-stimulus response.

When investigators examined the effects of manipulating stimulus intensity on 80-Hz ASSR phase, data revealed that phase increased, or correspondingly, latency and phase delay decreased as a function of stimulus intensity (Herdman & Stapells, 2001; John & Picton, 2000b; Lins et al., 1995; Picton et al., 2009).

Thus, the conclusions drawn by the above investigators reveal that the effects of stimulus intensity on amplitude and phase of the 40-Hz and 80-Hz ASSR follow the same trends. Response amplitude and phase increased, or correspondingly, latency and phase delay decreased as a function of stimulus intensity. In addition, no significant attenuation of the response occurs when stimuli--whether single or multiple--are 60 dB SPL are less.

Modulation Depth

Investigators agree that ASSR amplitude increased as a function of modulation depth (Picton, Skinner et al., 1987; Ross et al., 2000). However, there is no consensus as to the percentage of depth at which the maximum amplitude of the response is reached. Picton, Skinner et al. (1987) reported that AM responses showed minimal amplitude changes at modulation depths greater

than 50%, whereas Ross et al. (2000) reported nominal amplitude changes at modulation depths greater than 80%. With regard to phase, Picton and associates reported that AM phase responses did not change significantly with modulation depth, whereas Ross and colleagues reported that phase decreased slightly as modulation depth increased. Uncontrolled variables (e.g., sound delivery system and data acquisition) between these two studies could have contributed to the variance of the data, which may have masked the true phase values.

Picton and associates (1987) also investigated the relations between both AM and FM 40-Hz ASSR amplitude and phase when manipulating modulation depth alone and in conjunction with carrier frequency. While the amplitude of the response for both AM and FM tones increased with increasing modulation depth, AM responses increased in amplitude only up to 50%, whereas FM responses increased in amplitude up to 90%. The phase delay for AM and FM responses did not change significantly with modulation depth. However, the phase delays for FM responses were shorter than those of AM responses. When carrier frequency (0.5 to 4 kHz) and depth of modulation (10, 30 and 50%) were manipulated conjointly, the amplitude of AM and FM responses showed significant effects for both modulation depth and carrier frequency. Amplitude modulated responses at all carrier frequencies increased as the depth of modulation increased from 10 to 30%, and then reached an asymptote when modulation depth was increased from 30 to 50%. Frequency modulated responses, however, did not show the same tendency toward saturation. Furthermore, AM and FM responses were rank ordered according to carrier frequency, with 0.5 kHz showing the largest amplitude growth and 4 kHz the smallest when modulation depth was increased from 10 to 50%. The phase delays for AM and FM responses when manipulations of modulation depth and carrier frequency were combined

showed a significant effect only for carrier frequency, i.e., phase delays were shorter for higher than for lower carrier frequencies.

The effects of manipulating modulation depth on 80-Hz ASSR amplitude and phase have been documented in several studies. Lins and colleagues (1995) and John et al. (2001) conducted comprehensive studies on the effects of manipulating modulation depth on ASSR amplitude and phase to single AM tones. These researchers agree that ASSR amplitude increased as modulation depth increased when carrier frequencies were held constant. However, there is no consensus as to the percentage of depth at which the maximum amplitude of the response is reached. Lins et al. reported that AM responses increased linearly, but showed little variation in responses to modulation depths greater than 50%, whereas John et al. reported linear responses up to 100%. John et al. also investigated the effects of modulation depth on ASSR amplitude using FM stimuli. Frequency modulated response amplitudes showed the same tendency as AM response amplitudes as modulation depth increased. More notable, however, was the relation between AM and FM response amplitudes. One hundred percent AM stimuli elicited smaller response amplitudes than 50% FM stimuli, and 50% AM stimuli evoked similar response amplitudes to that of 20% FM stimuli. With regard to phase, Lins and associates (1995) reported that the phase of AM elicited responses increased with modulation depth, but showed nominal changes at modulation depths greater than 25%, whereas John et al. (2001) reported that both AM and FM phase delay did not change significantly with modulation depth. The lack of agreement between these two studies may be related to the use of different parameters for data acquisition and analyses of the 80-Hz ASSR waveforms.

John et al. (2001) also studied combinations of 100% AM and 25% FM tones modulated at frequencies near 80 Hz to determine if there was significant attenuation of the response when

tones were simultaneously presented to the same ear. Response amplitudes were recorded for AM and FM tones presented alone (baseline) and simultaneously with another AM or FM tone. Carrier frequencies at 1 kHz were modulated at 82.3 Hz and 2 kHz were modulated at 88.9 Hz. Comparisons revealed significant differences in amplitude (of about 20%) when FM tones were presented simultaneously with other AM or FM tones. The FM baseline amplitude at 1 kHz significantly decreased from its original value when FM tones at 1 kHz were presented simultaneously with other FM tones at 2 kHz. In addition, the amplitudes of the responses were attenuated when FM tones at 2 kHz were presented in combination with AM tones at 1 kHz. Although FM and AM stimuli are processed differently in the cochlea (Zwicker & Fastl, 1990), the 20% reduction of amplitude indicated very little overlap between the two different neuronal generators. This demonstrates that FM and AM responses are relatively independent. However, because of this amplitude reduction, the authors concluded that the efficiency of response detection might be compromised when recording FM responses together with other stimuli. No significant differences in amplitude were found when AM tones were presented simultaneously with other AM or FM tones. Unlike FM, AM responses are not susceptible to the presence of other stimuli, perhaps because their responses are mediated over a more narrow range (apical) of the basilar membrane. Phase delays were not significantly affected when either of the modulated tones were presented in combination with other AM or FM tones.

Similarly, Dimitrijevic, John, van Roon and Picton (2001) investigated the effects of IAFM (independent amplitude and frequency modulated) tones simultaneously presented to the same ear. The 0.75 kHz octave series (i.e., sequence of octave frequencies beginning at 0.75 kHz) was modulated at frequencies between 80.1 and 94.7 Hz for AM tones, and modulated at frequencies between 78.1 and 91.8 Hz for FM tones. Amplitudes were recorded for AM tones

with modulation depths of 100% and 50%, and for FM tones with a modulation depth of 20%. AM and FM tones were presented in combination. IAFM tones evoked two independent responses, one from the AM component and the other from the FM component, for each carrier frequency. Results revealed that response amplitudes for AM, FM and IAFM tones were larger in the lower frequencies than the higher frequencies. In addition, IAFM tones (100% AM and 20% FM) produced smaller response amplitudes than those obtained from simple AM stimuli. Response amplitudes were further attenuated when the AM component of the IAFM tone was changed from 100% to 50%, such that IAFM tones consisted of 50% AM and 20% FM. Furthermore, response amplitudes for both IAFM tones (100% and 50% AM) were smaller than those obtained from simple FM stimuli. Because of these reductions in amplitude, the authors concluded that the response detection of IAFM tones might be affected at low intensity levels.

Cohen et al. (1991) investigated response amplitudes for a single AM versus a single mixed modulated (MM, 100% AM, 20% FM) tone presented binaurally at 55 dB HL. Response amplitudes were measured at carrier frequencies between 0.25 and 4 kHz modulated at frequencies between 30 and 185 Hz. In general, response amplitudes to MM tones resembled those of AM tones across all frequencies. However, MM amplitudes were significantly larger than AM amplitudes for 2 and 4 kHz. Phase responses to MM and AM tones were similar. To extend these findings, John and Picton (2000a) investigated response amplitudes for multiple AM and MM (100% AM, 25% FM) tones presented binaurally at 50 dB SPL. A 0.75 kHz octave series was presented to the right and a 0.5 kHz octave series (i.e., sequence of octave frequencies beginning at 0.5 kHz) was presented to the left ear for AM and MM tones modulated at frequencies between 85 and 95 Hz. These results were in good agreement with data reported

by Cohen et al. Response amplitudes to MM tones evoked significantly larger responses than AM tones across all frequencies.

To further the initial studies of Cohen et al. (1991) and John and Picton (2000a), John et al. (2001) compared the effects of multiple AM and MM tones across a range of intensities lower than 50 dB SPL. Stimulus parameters were based on those previously reported in John and Picton (2000a). Responses were recorded to multiple AM (100%) and MM (100% AM, 25% FM) tones presented to each ear at 50, 40 and 30 dB SPL. Results revealed that response amplitudes to MM tones were significantly larger than AM tones, with the amplitudes to both AM and MM tones being larger in the middle frequencies and smaller at the extremes (i.e., 0.5 and 6 kHz). Amplitude responses to MM tones were on average 27, 40, and 24% larger than those obtained from simple AM stimuli at 50, 40 and 30 dB SPL, respectively. In addition, phase delays were later for AM tones than for MM tones. When the FM component of the MM tone was changed to 10%, such that the MM tones consisted of 100% AM and 10% FM, response amplitudes to MM tones with an FM depth of 10% were larger compared to MM tones with an FM depth of 25%, but only at an intensity of 50 dB SPL. John et al. again, concluded that overall response amplitudes to MM tones were larger than AM tones. In addition, MM tones with an AM depth of 100% and an FM depth of 25% evoke larger responses than AM tones when presented at 50, 40 and 30 dB SPL.

John, Dimitrijevic and Picton (2002) studied the effects of using exponential envelopes for modulating the amplitude and frequency of the carrier for 80-Hz ASSRs. Response amplitudes and phases were measured at carrier frequencies between 0.5 and 6 kHz and were modulated at frequencies between 78 and 95 Hz. To examine the effects of using exponential envelopes at both moderate and low intensities, all carrier frequencies were simultaneously

presented to both ears at intensities of 35 and 55 dB peak SPL (pSPL). Responses were recorded independently for AM (100%) and FM (25%) tones. Both types of stimuli were created and modulated using exponential sine functions where the power of the sinusoid ($\sin^N$) was between 1 and 4 (N). Clear enhancements of amplitude were evident in the responses for each of the different AM envelopes at both 35 and 55 dB pSPL, with 55 dB pSPL data showing larger amplitude increases at lower and higher carrier frequencies than enhancements that occurred in the middle carrier frequency region. Statistically different response amplitudes were obtained for AM exponential envelopes greater than 1 at 55 dB pSPL and to exponential envelopes using a power of 2 and 4 at 35 dB pSPL, compared to those obtained from simple AM stimuli. The effects of AM envelope on phase revealed that onset phase decreased or phase delay increased when the power of the sinusoid was increased. Unlike, AM, no clear enhancements (or decrements) of amplitude were evident for the different FM envelopes.

In addition, D'haenens et al. (2007) examined response amplitudes using MM versus AM^2/FM tones across a range of intensities. Response amplitudes were measured at carrier frequencies between 0.5 and 4 kHz and were modulated at frequencies between 82 and 106 Hz for the left ear and between 85 and 100 Hz for the right ear. To examine the effects of each of the stimuli used, all carrier frequencies were simultaneously presented to both ears at intensities ranging from 0 to 40 dB HL. Responses were recorded independently for MM (100% AM and 20% FM) and AM^2/FM (20% FM added to the exponential AM tone [with the exponential equal to 2] tones (John et al., 2001, 2002, 2004). Results revealed that amplitude responses to AM^2/FM tones were larger than those obtained from MM tones, with amplitudes being larger in the middle frequencies and smaller at the extremes (i.e., 0.5 and 4 kHz). In addition, amplitude

responses to AM^2/FM tones were larger than those obtained from MM tones for all stimulus intensities, except 0 dB HL.

Similarly, John et al. (2004) compared response amplitudes for four different types of modulation in two groups of infants. Response amplitudes and phases were measured at carrier frequencies between 0.5 and 4 kHz and were modulated at frequencies between 78 and 95 Hz. Responses were recorded independently for multiple AM (100%), FM (20%), MM (100% AM, 20% FM), and AM^2 tones. The "newborn" group of infants ranging from 37 to 42 weeks GA and were tested 72 hours after birth. The "older" group of infants ranging from 39.3 to 42 weeks GA and were tested three to 15 weeks after birth. Responses were also collected to FM tones in six newborn infants. Results revealed that amplitude responses to MM and AM^2 were statistically larger than those obtained from simple AM stimuli, with amplitudes being larger in the middle frequencies and smaller at the extremes (i.e., 0.5 and 4 kHz) for both younger and older infants. For the younger infants, the percentages of significant responses were 67%, 73%, 76% and 64% for AM, MM, AM^2 and FM tones, respectively. For the older infants, the incidences of significant responses were higher at 82%, 82%, and 84% for AM, MM and AM^2 tones, respectively. In relation to the AM response, average amplitudes across all carrier frequencies increased by 13% for the younger and 22% for the older infants for MM stimuli, and 16% for the younger and 13% for the older infants for AM^2 stimuli. Based on grandmean data for the two groups, the amplitudes of the responses for the older infants tested up to 15 weeks after birth were statistically larger than those recorded for the younger infants tested 72 hours after birth at 1, 2, and 4 kHz. In addition, based on simple AM stimuli, the effects of modulation type on phase revealed that onset phase decreased and phase delay increased for both the MM and AM^2 stimuli.

Likewise, Riquelme and colleagues (2006) compared response amplitudes for three different types of modulation in a group of newborn infants. Response amplitudes and phases were measured at carrier frequencies between 0.5 and 4 kHz and were modulated at frequencies between 25 and 98 Hz. Responses were recorded independently for multiple AM (100%), transposed tones (signals were multiplied by a half-wave rectified sine wave) and transposed noise (signals in which the spectra content was widened to include both a band of noise centered at a low and a high frequency). Although transposed tones were found to be superior at evoking ASSRs than AM tones, results revealed that transposed noise signals evoked larger amplitudes, produced higher response strength and detected responses faster than did transposed tones.

Thus, investigators agree that the effects of modulation depth on amplitude of the 40-Hz and 80-Hz ASSR follow the same trends. Although, response amplitude increased as a function of modulation depth, there is no consensus as to the percentage of depth at which the maximum amplitude of the response is reached. Research has revealed that MM tones (100% AM and 25% FM), AM^2 (exponential stimuli) and transposed noise signals evoke larger responses than AM tones alone.

Phase

As evidenced from the above studies, setting and selecting the depth of modulation is very important for response detection. Because MM tones with an AM depth of 100% and an FM depth of 25% yield the largest response amplitudes (Cohen et al., 1991; John et al., 2001), setting and selecting the relative phase between the AM and FM components of MM tones is equally important for optimal response detection. John et al. (2001) studied the effects of changing the relative phase between the AM and FM components of MM tones in adults. The amplitudes of the responses were recorded separately for AM, FM and MM tones, with the 0.5 kHz octave

series presented to the right ear and the 0.75 kHz octave series presented to the left ear. The phases of the FM component of MM tones were systematically modified using four different relative phases of 0°, 90°, 180° and 270°. The phase of the AM component was fixed. Results revealed that response amplitudes for MM tones with FM phases at 0° (or 360°) and 270° (-90°) were significantly larger than responses to AM tones alone. Furthermore, the effects of FM phase on the MM response were consistent across all frequencies except 6 kHz. To further define the largest MM response, John et al. examined the relative phases of 0°, 45°, 270° and 315° using the 0.5 kHz octave series. Results revealed that the largest response amplitude occurred for MM tones with FM phases of 315° across all frequencies except 0.5 kHz. Thus to yield the largest responses, John et al. recommended phases for MM tones be set at 45°, 315°, 315°, 315°, for 0.5, 1, 2, and 4 kHz respectively.

In summary, for optimal response detection setting the relative phase between the AM and FM components of MM tones help to produce the largest combined response. Findings reveal that the MM response was generally largest when the relative phases for the FM components were set at 45°, 315°, 315°, and 315°, for 0.5, 1, 2, and 4 kHz respectively.

Carrier Frequency

Investigators agree that response amplitude, to a single-stimulus 40-Hz ASSR, decreased and phase increased, or correspondingly response latency decreased as a function of frequency (Galambos et al., 1981; Klein, 1983; Kuwada et al., 1986; Rodriguez et al., 1986; Ross et al., 2000; Szyfter et al., 1984).

The potential usefulness of recording single- and multiple-stimulus 80-Hz ASSRs was first examined by Lins and Picton (1995). Lins and Picton examined the effects of carrier frequency on response amplitude using two conditions in which four AM carrier frequencies

were presented singly and simultaneously to the right ear. Carrier frequencies at 0.5, 1, 2, and 4 kHz were modulated at 81, 89, 97 and 105 Hz, respectively. Results revealed no significant difference in the amplitudes of the responses between the two monotic stimulus conditions. To extend these results, Lins and Picton recorded responses to six stimulus conditions in which four AM carrier frequencies were presented singly and simultaneously to one ear, and simultaneously to both ears. Carrier frequencies at 0.5, 1, 2, and 4 kHz were modulated at 81, 89, 97 and 105 Hz for the right ear, and modulated at 77, 85, 93, and 101 Hz for the left ear. Results revealed no significant differences between the amplitudes for each of the stimulus condition or carrier frequencies.

However, several studies have demonstrated a reduction in amplitude when multiple stimuli less than a half an octave apart are simultaneously presented to the same ear. Lins and Picton (1995) studied interactions between multiple stimuli with the same carrier frequency presented at different modulation frequencies. Responses were recorded to 1 kHz AM tones presented at 60 dB SPL modulated at frequencies of 39, 49, 81 and 93 Hz. Amplitudes were measured to 1 kHz tones at 39 and at 81 Hz 'alone', to 1 kHz tones with 'similar' modulation frequencies (e.g., 39 and 49 Hz), to 1 kHz tones with 'different' modulation frequencies (e.g., 39 and 81 Hz) and to all 1 kHz tones presented 'together'. Results revealed that the amplitudes of the responses in the 'alone' condition were significantly larger than those obtained in the 'together' condition. Regardless of whether the modulation frequencies of the two stimuli were 'similar' or 'different', when two tones of the same frequency were presented to the same ear the amplitude of the response was reduced by 19%. When all stimuli were presented 'together' the response was attenuated by 57%.

John et al. (1998) studied interactions between multiple stimuli with different carrier frequencies presented at different modulation frequencies. Responses were recorded to two AM tones, a 1 kHz probe tone modulated at 80.9 Hz and a masker tone modulated at 96.9 Hz, each presented at 60 dB SPL. The masker tone was varied with experimental condition: 0.5, 0.75, 0.9, 1, 1.05, 1.1, 1.2, 1.35, 1.5 and 2 kHz. The 1 kHz probe tone was presented alone and then simultaneously with a masker tone. Results revealed that the amplitudes of the responses to the 1 kHz probe tone were attenuated when the masker frequency was either higher or lower than the 1 kHz probe tone. When the 1 kHz probe tone and the masker were equal, the amplitude was larger than those responses to frequencies slightly below (i.e., 0.95) and slightly above (i.e., 1.05) the probe tone. However, there was no significant attenuation of the response when the two carrier frequencies presented were separated by more than half an octave. To examine if the same results regarding carrier frequency separation would extend to stimulus conditions of more than two AM tones, John et al. (1998) created a second paradigm which utilized 1 and 2 kHz AM tones presented alone and in combination with other carrier frequencies to create two-, four- and eight-tone stimulus conditions. Carrier frequencies were separated by either half an octave, or by one octave. John and colleagues concluded there was no significant attenuation of the response as long as the carrier frequencies presented were separated by more than half an octave.

Likewise, Herdman and Stapells (2001) found similar results when the differences between various monaural and binaural stimulus conditions were investigated. Response amplitudes were elicited by AM carrier frequencies at 0.5, 1, 2, and 4 kHz modulated at frequencies between 77 and 105 Hz. Results revealed that when stimulus intensities were held constant, 80-Hz ASSR amplitude did not vary significantly when single AM tones were presented separately or when multiple AM tones were presented simultaneously to one or both

ears. To evaluate more closely, Picton et al. (2009) recorded responses to multiple stimulus conditions in which four AM tones were presented singly and simultaneously to one ear, and simultaneously to both ears. Responses were recorded to AM tones at .5, 1, 2, and 4 kHz. Modulation frequencies ascended with increasing carrier frequency. In addition, modulation frequencies for the corresponding carriers for the left ear were slower than those for the right ear. When responses were measured singly to each of the eight stimuli presented simultaneously to each ear, there was a significant increase in the amplitude of the response, relative to what was obtained when multiple stimuli were presented to both ears. However, this effect was not obtained when responses were examined independent of the effects of multiple stimuli. Tones of 1 kHz were presented to each ear alone and presented simultaneously to both ears. No significant differences were found in the amplitudes of the responses in the two ears. When responses were measured to multiple stimuli, amplitudes to both stimulus conditions, multiple stimuli presented to one ear and to both ears simultaneously, produced a U-shaped curve. However, it was only when multiple stimuli were presented to one ear that the amplitudes at 1 and 2 kHz were significantly smaller than those obtained at 0.5 and 4 kHz. The authors concluded that this response pattern is likely due to the masking effect of low frequency stimuli and an extra inhibitory effect (most likely central in origin) of high frequency stimuli (John et al., 1998; Ross et al., 2003).

When the effect of carrier frequency on ASSR phase was investigated, results from Herdman and Stapells (2001) and Picton et al. (2009) were in good agreement with data reported by Lins and associates (1995), who assert that phase increased as AM tones increased from 0.5 to 4 kHz.

Thus, investigators agree that the effects of carrier frequency on amplitude and phase of the 40-Hz and 80-Hz ASSR follow the same trends. The conclusion drawn by the above investigators was that response amplitude decreased and phase increased, or correspondingly response latency decreased as a function of frequency. In addition, no significant attenuation of the response occurred when carrier frequencies presented are separated by more than half an octave. Moreover, ASSRs to single stimuli do not vary significantly in their amplitude across carrier frequencies, whereas ASSRs to multiple stimuli are either equal in amplitude across carrier frequencies or are larger at the midfrequencies.

Modulation Frequency

Transient Stimuli

The first amplitude rate series was demonstrated by Galambos et al. (1981), who assert that the amplitude of the response peaked at 40 Hz, with a smaller peak evident at its sub-harmonic at 20 Hz when TBs of 0.5 kHz were modulated at frequencies between 10 and 60 Hz. When this study was replicated, Stapells et al. (1984) reported practically identical results. The amplitude of the response was found to be greatest between 40 and 45 Hz, with a second harmonic component at 20 Hz. Likewise, Linden et al. (1985) found the amplitude of the response was largest between 30 and 50 Hz, with variable sub-harmonic peaks at rates between 10 and 20 Hz. Similarly, Suzuki and Kobayashi (1984) and later Azzena et al (1995) reported the ASSR peaks at 40 Hz when clicks were presented at rates between 7.9 and 60 Hz. Correspondingly, Stapells et al. (1987), Stapells et al. (1988) and later Picton et al. (2003) reported the highest amplitude of responses was obtained at 40 Hz when TBs were presented at rates between 9 and 80 Hz. These results are in concordant with Pastor et al. (2002) who studied monaural trains of stimuli at 12 different stimulus rates between 12 and 60 Hz. Moreover, in a related study in which ASSRs

were recorded by magnetoencephalographic (MEG) field patterns, Hari et al. (1989) reported that responses were highest in amplitude at a rate of 40 Hz when clicks were presented at rates between 10.1 and 70 Hz. These findings complemented investigations which demonstrated similar adult amplitude functions when modulated tones were used. In addition, investigators agree that apparent latency decreases as stimulus repetition rate increases. Table 26 shows the comparison of apparent latencies calculated for tones presented at repetition rates ranging from 19 to 450 Hz.

Unlike the adult amplitude function, the effects of modulation rate on ASSR amplitude in newborns and young children were variable. Suzuki and Kobayashi (1984) reported that responses were highest in amplitude at a rate of 20 Hz in young children ranging from 3 months to 6 years of age during sleep when clicks were presented at rates between 10 and 50 Hz. Comparable results were reported by Fifer (1985) when 0.5 kHz tone pips were presented at rates between 5.1 and 40.1 Hz in newborn infants. Conversely, Stapells et al. (1988) found no consistent amplitude peak when TBs at 1 kHz were presented at rates between 9 and 59 Hz in infants 3 weeks to 28 months old.

Steady-State Stimuli

In accordance with the results in the above-mentioned studies, research using modulated tones confirms that the amplitude of the ASSR peaks primarily in adults between 40 and 50 Hz. Rees et al. (1986) reported responses were highest in amplitude at a rate of 40 Hz, with a smaller peak evident at its sub-harmonic between 5 and 20 Hz when 1 kHz AM tones were modulated at frequencies between 2 and 400 Hz. Similar results were reported previously by Rees (1982). Picton, Skinner et al. (1987) reported responses were highest in amplitude between 2 and 7 Hz and between 27 and 55 Hz for 1 kHz AM tones, and between 3 and 7 Hz and 20 and 55 Hz for 1

kHz FM tones. Likewise, Lins and Picton (1995) found the largest ASSR amplitude was recorded at 39 Hz when AM tones modulated at 39, 49, 81 and 93 Hz. Comparable results were reported by Levi et al. (1993), who assert ASSRs were optimized using a modulation frequency of 40 Hz when 0.5 and 2 kHz AM tones were modulated at frequencies between 10 and 80 Hz. Correspondingly, Kuwada et al. (1986) revealed a characteristic amplitude peak between 40 and 45 Hz when 1, 2, and 4 kHz AM tones were modulated at frequencies between 25 and 350 Hz. Likewise, Cohen et al. (1991) reported responses were highest in amplitude at a frequency near 45 Hz when 0.25, 0.5, 1, 2, and 4 kHz AM (100%) and MM (AM 100%, FM 20%) tones were modulated at frequencies between 30 and 190 Hz.

In addition to the characteristic peak around 45 Hz, Cohen and colleagues noted that another peak in the amplitude function was visible between 85 and 110 Hz. These results were comparable to works by Kuwada et al. (2002) who revealed a second amplitude peak in the region between 80 to 100 Hz when 1 kHz AM tones were modulated between 26 and 261 Hz. Lins et al. (1995) reported the amplitude of the ASSR peaked between 83 and 91 Hz when AM tones were modulated at frequencies between 67 and 111 Hz. Likewise, Ross et al (2000) reported a secondary peak visible at 80 Hz when 0.25 kHz AM tones were modulated at frequencies between 10 and 100 Hz. Similarly, a study by Artieda and colleagues (2004) revealed a second amplitude peak in the region between 80 and 120 Hz when AM tones were increased linearly in frequency from 1 to 120 Hz (‘chirp’). Resembling findings associated with transient stimuli, investigators agree that apparent latency decreases as modulation frequency increases.

Table 26 Mean Apparent Latency Values for Transient and Steady-State Stimuli

Study	Stimuli	Rate (Hz)	0.25	0.5	1	2	4 kHz	Clicks
Transient Stimuli								
Stapells et al. (1987)	TB	19-29		74.7				
Hari et al. (1989)	Clicks	30-70						53.9
Stapells et al. (1987)	TB	30-54		41.12				
Picton et al. (2003)	TB	32-64			29.0			
Stapells et al. (1984)	TB	40-46		29.3	25.3	20.3	20.3	
Steady-State Stimuli								
								Noise
Picton, Skinner et al. (1987)	AM	3-7			149			
Ross et al. (2000)	AM	20	72.0					
Ross et al. (2000)	AM	40	48.0					
Kuwada et al. (1986)	AM	25-55			31.0			
Picton, Skinner et al. (1987)	AM	27-55			37.2			
Picton, Skinner et al. (1987)	FM	27-55			37.8			
Kuwada et al. (2002)	AM	26-46			27.0			
Cohen et al. (1991)	MM	30-60	31.6	33.0	24.8	28.9	28.6	
Purcell et al. (2004) [a]	AMWN	35-55						24.3
John et al. (2001)	AM	75-95		30.9	24.8	15.4	13.1	

Table 26 continued.

John et al. (2001)	FM	75-95		27.6	22.4	12.3	18.0	
Ross et al. (2000)	AM	80	26.0					
Purcell et al. (2004) [a]	AMWN	75-90						11.2
John & Picton (2000b)	AM	80-100		21.5	18.9	16.7	16.1	
Lins et al. (1995)	AM	80			19.0			
Lins & Picton (1995)	AM	80			15.0			
Cohen et al. (1991)	MM	90-125	11.6	12.7	13.0	9.4	8.9	
John & Picton (2000b)	AM	150-190		12.2	10.3	7.8	6.9	
Purcell et al. (2004) [a]	AMWN	110-450						8.8
Kuwada et al. (2002)	AM	160-260			8.0			
Kuwada et al. (1986)	AM	100-350			7.5			

Note: Comparative survey of mean apparent latency values for transient and steady-state stimuli. Apparent latency is measured in msec.
[a] Potentials were referred to as the envelope following response (EFR).

Unlike the adult amplitude function, the effects of modulation frequency on ASSR amplitude in infants and young children were variable. Riquelme et al. (2006) reported that responses were highest in amplitude at between 25 and 37 Hz in infants when 0.5, 1 and 2 kHz transposed tones were modulated between 25 and 88 Hz. In contrast, Rickards et al. (1994) reported the amplitude of the ASSR peaks between 72 and 97 Hz in infants when 0.5, 1.5 and 4 kHz MM tones were modulated between 40 and 190 Hz. Likewise, Levi et al. (1993) revealed that ASSRs were optimized using 80 Hz modulation in infants when 0.5 and 2 kHz AM tones were modulated at frequencies between 10 and 80 Hz. Similarly, Aoyagi et al. (1993) found the most desirable modulation frequency in young children 2 to 4 years of age to be between 80 and 100 Hz when 1 kHz AM tones were modulated at frequencies between 2 and 200 Hz. These results were confirmed a year later by Aoyagi et al. (1994) who found the mean CSM was highest at 80 Hz in children 4 months to 15 years of age. These results were different from those obtained later by Pethe and colleagues (2004), who assert that ASSR amplitude peaks at low modulation frequencies (i.e., 40 Hz) in children 3 years and over and peaks at high modulation frequencies (i.e., 80 Hz) in young children 3 years and under.

In summary, the effects of stimulus intensity, modulation depth and carrier frequency on amplitude and phase of the 40-Hz and 80-Hz ASSR follow the same trends: (a) response amplitude and phase increased, or correspondingly, latency and phase delay decreased as a function of stimulus intensity; (b) response amplitude increased as a function of modulation depth, however, there is no consensus as to the percentage of depth at which the maximum amplitude of the response is reached, and (c) response amplitude decreased and phase increased, or correspondingly response latency decreased as a function of frequency.

Corresponding research concerning the stimulus parameters used on 80-Hz ASSRs has determined that: (a) there was no significant attenuation of the response when carrier frequencies presented are separated by more than half an octave, and stimuli are 60 dB SPL or less; (b) there were no significant differences found in ASSRs across frequencies between single- and multiple-stimulus conditions; (c) mixed modulated tones with an AM depth of 100% and an FM depth of 25% evoked larger responses than AM tones alone; (d) response amplitudes were largest when evoked by MM tones (100% AM and 25% FM), AM^2 (exponential stimuli) and transposed noise signals than those obtained from AM tones alone; (e) MM tones yielded the largest response when phases are set at 45°, 315°, 315°, 315°, for 0.5, 1, 2, and 4 kHz respectively, and (f) regardless of the type of stimulation a modulation frequency of 40 Hz is most effective in evoking the ASSR in adults; however, the effects of modulation frequency on ASSR amplitude in newborns and young children are variable.

This chapter subsection addressed the effects of stimulus factors on response amplitude and latency (or phase) when recording AEPs evoked by transient and steady-state stimuli. Subsection 3.6 will detail the effects of natural sleep on AEPs evoked by transient and steady-state stimuli, and will discuss the optimal subject state for effective MLR, LLR and ASSR recordings.

3.6 THE EFFECT OF NATURAL SLEEP ON AEPS

Auditory evoked potentials are elicited when neural activity in the auditory pathway responds to complex sounds. Because this response is extremely small compared to ongoing physiologic and non-physiologic background noise, it is customary during AEP measurement to encourage

relaxation or natural sleep. However for some AEP measurements, waveform morphology changes with level of consciousness--from wakefulness into light and then into deeper stages of natural sleep. Thus, optimal subject state varies for each AEP. Although the ABR is virtually unaffected during sleep, all cortical responses are drastically modified during different stages of sleep. This chapter subsection will address the differential effects of natural sleep on MLR, LLR and ASSR amplitude, latency (or phase).

3.6.1 Transient Stimuli

3.6.1.1 MLR

As previously described, MLRs obtained in infants and young children are only intermittently obtained during certain stages of sleep (Kraus et al., 1985; Okitsu, 1984). According to Kraus, McGee and Comperatore (1989) detectability of wave P_a was highest during wakefulness, stage 1, and during rapid eye movement (REM) sleep in young children ranging in age from four to nine years. In contrast, detectability of wave P_a was variable during stages 2 and 3, and was poorest during stage 4. Detectability in stage 4 improved--from 4.2 to 54.4%--in older children ranging in age from seven to nine years. Comparable results were found by Collet, Duclaux, Challamel, and Revol (1988), who reported that N_a-P_a amplitude was largest during active sleep (during REM) and smallest during quiet sleep (stages 2 through 4 of NREM or slow wave sleep [SWS]).

Although the effects of sleep on MLR amplitude in adults tended to be somewhat variable, the most consistent finding was that changes in N_a-P_a and P_a-N_b amplitude were found to be minimal in adults during all stages of natural sleep (Mendel, 1974; Mendel & Goldstein, 1971; Mendel & Kupperman, 1974; Picton et al., 1974). These data are also supported later by

Erwin and Buchwald (1986), which showed no significant amplitude changes as sleep shifted from NREM to REM sleep. Other investigations have shown that P_a-N_b amplitude was significantly reduced during NREM sleep (Jones & Baxter, 1988; Okitsu, 1984; Osterhammel et al., 1985); while still others found slightly different results in which P_a-N_b amplitude was largest during light sleep (stages 2 and REM) and smallest during deep sleep (stages 3 and 4) (Deiber, Ibañez, Bastuji, Fischer, & Mauguière, 1989).

Thus, in young children the MLR is only present in certain stages of sleep. Sleep stage 4 is the most unfavorable for recording in young children; however, MLR detectability improves with age. For adults, the majority of investigators agree that changes in the MLR with sleep are minimal with some reduction in amplitude, but can be reliably recorded during light sleep.

3.6.1.2 LLR

As previously described, responses obtained in both children and adults are affected by state of consciousness such that natural sleep has a pronounced effect on LLR waveforms (Weitzman & Kremen, 1965; Williams et al., 1962). There have been only a few investigators that have attempted to evaluate the effects of natural sleep on various components of the LLR in infants and young children. Findings revealed that N_1 and P_2 amplitudes were significantly smaller during REM than during NREM sleep (Rapin & Graziani, 1967; Weitzman, Fishbein, & Graziani, 1965). Likewise, studies have reported N_2 amplitude was smallest during REM than any other stage of sleep in infants and young children (Ornitz, Ritvo, Carr, Panman, & Walter, 1967; Weitzman et al., 1965). Conversely, Suzuki and Taguchi (1968) found that P_1, N_1 and P_2 latencies increased during sleep in young children.

In contrast to the relatively limited study of the effects of sleep on the LLR in infants and young children, several investigators have attempted to evaluate adults, however outcomes

reported were variable. Williams et al. (1962) and later Weitzman and Kremen (1965) reported that P_1 amplitude increased as adults shifted from wakefulness into deeper stages of natural sleep. Other studies, undertaken by Erwin and Buchwald (1986) and later by Jones and Baxter (1988) revealed a complete loss of wave P_1 in sleep stages 2 through 4, which then reappeared in REM sleep. The same high degree of variable performance was found among studies reporting the effects of sleep on N_1 and P_2 amplitudes. Williams et al. revealed that N_1 and P_2 amplitudes were significantly smaller during REM than any other stage of sleep. A few years later, a study undertaken by Weitzman and Kremen reported just the opposite, that is, P_2 amplitudes were significantly greater in REM than any other stage of sleep. Interpretation of these discrepancies is not easy since all of the above-mentioned studies used auditory clicks. However, the most consistent finding regarding the effects of sleep on LLR amplitude was that N_2 amplitude was reportedly smallest during REM than any other stage of sleep in adults (Ornitz et al., 1967; Weitzman & Kremen, 1965; Williams et al., 1962). In addition, P_1, N_1 and P_2 latencies to acoustic clicks were stable from wakefulness to sleep (Fruhstorfer & Bergström, 1969; Kevanishvili & Von Specht, 1979; Weitzman & Kremen, 1965).

It is difficult to draw specific conclusions about sleep effects on LLR amplitude in infants, young children and adults based on the limited and aggregate of information. However, in infants and young children study outcomes revealed that LLR components were significantly reduced in REM than any other sleep stage. In adults, there was a high degree of variable performance among studies reporting the effects of sleep on N_1 and P_2 amplitudes. However, study outcomes consistently revealed that N_2 amplitude was smallest during REM than any other stage of sleep.

3.6.2 Steady-State stimuli

3.6.2.1 ASSR

Results of earlier research on the 40-Hz response, such as that of Shallop and Osterhammel (1983) revealed that 40-Hz response amplitudes in infants were significantly different when evoked during natural sleep than while awake. This finding complemented later research that revealed reliable 40-Hz responses were difficult to obtain in infants and young children during natural sleep (Maurizi et al., 1990; Stapells et al., 1988). Levi et al. (1993) was the only study retrieved that examined the effect of natural sleep on ASSRs in infants. Levi and colleagues reported that mean coherence estimates increased as a function of modulation frequency when AM tones were varied from 10 to 80 Hz. These authors concluded that coherence estimates were most stable and highest at 80 Hz modulation in 1-month old infants during natural sleep.

In adults, the effects of sleep on the 40-Hz ASSR are known to be large; the reduction in response amplitude can be as much as 50% when transitioning from wakefulness to natural sleep (Brown & Shallop, 1982; Cohen et al., 1991; Galambos et al., 1981; Jerger, Chmiel, Frost, & Coker, 1986; Picton et al., 2003; Shallop & Osterhammel, 1983; Suzuki, Kobayashi, & Umegaki, 1994). Amplitude reduction during drowsiness has also been inferred by observation in several other studies that have investigated the accuracy of estimating threshold using the 40-Hz ASSR measurement (Dauman, Szyfter, Charlet de Sauvage, & Cazals, 1984; Klein, 1983; Linden et al., 1985; Picton, Vajsar, Rodriguez, & Campbell, 1987; Sammeth & Barry, 1985; Stapells et al., 1988; Szyfter et al., 1984). Although response amplitudes were reduced during natural sleep in adults, the morphology was similar with a characteristic amplitude peak at a frequency near 40 Hz (Aoyagi et al., 1993; Cohen et al., 1991; Linden et al., 1985; Stapells et al., 1988) and a second component visible between 80 and 100 Hz (Cohen et al., 1991). Conversely, Griskova,

Morup, Parnas, Ruksenas, and Arnfred (2007) reported results somewhat at variance with the above-mentioned studies. Griskova et al. examined the effects of level of arousal on the 40-Hz ASSR. Stimuli were presented while subjects were reading a self-selected book (i.e., high arousal condition) and while subjects were resting (i.e., low arousal condition). Results showed an increase of amplitude during the low arousal condition compared to the high arousal condition.

When the effects of sleep on phase were examined, several investigators reported no systematic effect of sleep on 40-Hz ASSR phase, or correspondingly, latency and phase coherence (Cohen et al., 1991; Jerger et al., 1986; Linden et al., 1985). However, results based on the application of non-negative multi-way factorization (NMWF) and inter-trial phase coherence (ITPC) revealed an increase in phase of the 40-Hz ASSR when subjects were relaxed in a resting state compared to when subjects were alert and reading a self-selected book (Griskova et al., 2007).

Thus, in infants and young children it is difficult to obtain reliable 40-Hz ASSRs. For adults, the effects of modulation frequency on ASSR amplitude are similar during wakefulness and in natural sleep, however, changes in the 40-Hz amplitude with sleep are significant, but can be reliably recorded during light sleep.

In summary, the MLR and LLR amplitude in children are affected by state of consciousness such that sleep has a pronounced effect on waveform morphology. The MLR in adults, has some reduction in amplitude, but can be reliably recorded during light sleep. In contrast, based on the aggregate of information, it is difficult to draw specific conclusions about the effects of sleep on LLR amplitude in adults. Although several studies have examined the effects of repetition rate on ASSR amplitude and latency in adults while asleep, these

investigations have only studied those modulation frequencies 10 Hz and above (Levi et al., 1993; Picton et al., 2003) However, to date, no studies have examined the effects on response measurements at very low modulation frequencies, lower than 10 Hz or correspondingly, the repetition rates characteristic of the LLR.

3.7 OVERVIEW

The preceding sections/subsections provide a complete overview of the neuroanatomical development of the peripheral and central auditory system; a comprehensive outline of age-related morphological changes in AEP amplitude and latency (or phase) from infancy to adulthood; a thorough examination across studies into age-dependent stimuli and recording factors for AEPs, and a theoretical framework for examining changed cortical activity by utilizing sleep. This literature review has identified several areas that are largely uncharted and warrant investigation. These key areas, highlighted below, comprise the foundation for this study's rationale:

- The maturation sequences of the MLR and LLR have not been well characterized in infants and young children. A particular challenge for researchers and clinicians alike are the potential difficulties, if not ambiguities, of wave identification over the course of maturation. The identification of EP waveforms thus is relatively difficult, and even more so when looking across development, and when there is focal head injury. This short-coming derives from the way AEPs are traditionally analyzed, which is dependent largely upon subjective waveform identification (i.e., examiner judgment). Thus, there is a need for a substantially different way to evaluate AEPs themselves and for the purposes of

looking across normal and injured brain development. The steady-state-analysis approach potentially provides a more analytical and objective approach whose advantages may well serve such interests as tracking maturation changes and/or effects of brain injury.

- ASSR amplitude and latency functions have not been completely characterized in adults and are ill-defined in infants and young children. Although a few investigators have examined response amplitudes and latencies at modulation frequencies below 10 Hz (or correspondingly, the latencies characteristic of the LLR), this area has not been investigated thoroughly. Investigations clearly demonstrate that ASSR amplitude in infants and young children are different from an adult. However, from the aggregate of ASSR information specific changes in amplitude and latency measurements have not been well characterized at different modulation frequencies in children. Thus, there is a need to profile ASSR amplitudes in children and in adults over a wide range of repetition rates, specifically those that were expected to represent the general ranges of traditional AEPs.
- ASSR measurements are not completely characterized in adults or children in sleep. Although several studies have examined the effects of repetition rate on response amplitude and latency during sleep, these investigations have only explored those modulation frequencies 10 Hz and above (Levi et al., 1993; Linden et al., 1985; Picton et al., 2003). The effect of sleep on ASSR is unclear for very low modulation frequencies, lower than 10 Hz or correspondingly, the repetition rates characteristic of the LLR. Interest in such sleep results derives from the necessity of keeping subjects fully alert during testing, especially young children in assessing the more rostrally generated

potentials. Thus, there is a need to examine the effects of repetition rate on response amplitude during sleep in adults (first), which will then help predict the level of concern about the effects of sleep in children.

Thus, this study was designed to utilize a steady-state stimulus and analysis technique for several reasons. First, to permit characterization of subject age-related amplitude values, for one particular age group of children and in adults, to define the repetition rate(s) which evoke(s) maximal response amplitude as a function of age. Second, to allow examination of the effects of repetition rate on response amplitude during natural sleep, to demonstrate if results differ from those obtained when adults are awake.

4.0 METHODS

4.1 SUBJECTS

There were 37 young normal-hearing females that participated in this study. Subjects were six through nine (n =12) and 18 through 35 years of age (n =25). To minimize gender effects, subjects were all females and were tested via their right ears (cf. Subsections 3.11, 3.12 and 3.13). No subjects had a personal history of otological or neurological disorders as reported by parents of children or self-reported by personal interview. Each subject demonstrated normal middle ear function in both ears as defined by unremarkable otoscopic and tympanometric results, as defined below. All subjects had normal hearing sensitivity in both ears (to corroborate the assumption of an overall intact auditory nervous system), defined as thresholds of 15 dB HL or better for pure tone octave frequencies between 0.25 and 8 kHz (see below). In addition, all subjects demonstrated the main component waves of transient AEP response measurements in the three major latency groups.

Study participants were recruited in accordance with guidelines established by the University of Pittsburgh Institutional Review Board (IRB). Normal hearing children six to nine years of age were recruited from the Audiology and Communication Disorders Department at Children's Hospital of Pittsburgh. Because the investigators were not directly involved in the care of most patients, we relied on audiologists to introduce our study to patients with normal hearing who are under their care. Clinicians supervised by Dr. Diane Sabo introduced the study

to appropriate patients. Patients that indicated an interest in learning more about this research study were given a flyer (cf. Appendix A) which briefly described the study and listed the researchers contact information. Recruitment activities also included posting local flyers and notices on campus and at local day cares. The parents of the children contacted the investigators by telephone if they were interested in discussing the possibility of their child's participation in the study. In addition, recruitment included tapping the pool of undergraduate and graduate females who were students at the University of Pittsburgh and/or from classes offered by the Department of Communication Science and Disorders. Students were recruited via verbal announcements in staff meetings and in undergraduate and graduate Communication Science and Disorder classes (cf. Appendix B).

A brief screening either in person or by telephone (cf. Appendix C) was conducted on all potential participants to rule out individuals with self-reported auditory deficits, history of head trauma, neurological disorders, and individuals who presented with symptoms suggestive of retrocochlear pathology, all of which could potentially affect the amplitude and latency of AEPs evoked by transient and steady-state stimuli. Individuals who passed the screening requirements were offered enrollment in the study, and participant responsibilities were then described and informed consent obtained. Remuneration was provided for participants who complete part or all experimental testing.

Ideal study participants were children less than six years of age because of the substantial immaturity of their cerebral cortices (cf. Subsection 3.3.7). However, AEP recordings are often difficult to obtain in infants and children up to five years of age because they are not mature enough to execute specific tasks required for this study and/or remain adequately quiet. Consequently, children less than six years of age were excluded from this study. Children six to

nine years of age were chosen because they were still physiologically immature, but at an adequate developmental stage to appropriately perform tasks intended to hold their attention while recording (Yendovitskaya, 1971). Individuals having a personal history of otological or neurological disorders, as well as those of male gender were excluded from this study.

4.2 INSTRUMENTATION

Pure-tone audiometry was conducted with subjects seated in a double-walled sound-isolated room (Industrial Acoustics Company, Inc) in which the ambient noise level did not exceed limits established by ANSI Standards (S3.1-1991). Hearing sensitivity was measured on a Beltone 2000 audiometer, which was electroacoustically calibrated to ANSI S3.1-1991. Objective measurement of middle ear status was measured on either a WelchAllyn MicroTymp 2 or a Grason-Stadler GSI 33 Tympanometer. Transient and steady-state AEP recordings were conducted using a prototype of an evoked response system (Smart EP ASSR) manufactured by the Intelligent Hearing Systems (IHS), Miami, FL. All calibration was conducted prior to subject recruitment. Listening checks of all equipment were conducted before each testing session. All equipment used in the study was performed using Food and Drug Administration (FDA) approved electroacoustic instrumentation and which is commonly used clinically with children and adults.

4.3 PROTOCOL

4.3.1 Stimuli

The stimuli for transient and steady-state recordings were generated using IHS SmartASSR evoked potential software. The SmartASSR software regularly distributed provided stimulus control and analysis sufficient to evaluate ASSRs down to repetition rates of less than 40 Hz. To permit testing much lower rates, the company generously provided alternative versions of control modules that set the repetition rate, response windowing, and other proprietary parameters read by Smart ASSR upon initialization. The use of manufacturer-supplied software (over third-party custom software) assured operation without significant deviation from the instrumentation that had receive extensive use and evaluation in the clinical instrument marker, as well as in research laboratories, and approved by the FDA. Similarly, conventional transient response testing was accomplished using IHS' SmartEP software, implement on the same platform. The stimuli for the ABR, MLR and LLR were 1 kHz TBs. This was chosen for purposes of a uniform comparison across latency ranges and conditions using a mutually effective stimulus. The transient AEP literature provides limited guidance for systematically choosing TB parameters over the broad range of repetition rates used in this study. A rule-based approach was sought by which to systematically vary rise and fall, and overall duration as a function of repetition rate. Namely, TB envelope parameters were adjusted so as to be increased by 1.414X with each octave decrease in repetition rate, starting with 4 msec duration and 1 msec rise and fall for a repetition rate of 20 Hz (for the ABR), 11 msec duration and 2.8 msec rise and fall for a repetition rate of 10 Hz (for the MLR), and 45 msec duration and 11 msec rise and fall for a repetition rate of 0.63 Hz modulation (for full power integration of the stimulus for LLR). The

envelope was the extended cosine, to ensure abrupt on-set (for excellent neural synchrony) while, again, maintaining strong frequency specificity.

The stimuli for steady-state recordings were repeated TBs (extended Cosine window with 50 msec duration) at rates at octave or nearly octave intervals from 0.75 Hz. [*Note: the initial design of the study called for the lowest rate to be 0.625 Hz (i.e. $\simeq$ 0.63, as truncated in the SmartEP program), but, as explained below (cf. Subsection 4.3.3.2), it proved to be 0.75 Hz for the ASSR.] The same rule-based approach (above) was applied to the remaining ASSR repetition rates used in this study. The remaining envelope parameters were as follows. A 45 msec duration and 11 msec rise and fall for a repetition rate of 0.75 Hz modulation (same parameters used above for the transient LLR), 32 msec duration and 8 msec rise and fall time for a repetition rate of 1.25 Hz, 23 msec duration and 5.6 msec rise and fall time for a repetition rate of 2.5 Hz, 16 msec duration and 4 msec rise and fall time for a repetition rate of 5 Hz, a 11 msec duration and 2.8 msec rise and fall time for a repetition rate of 10 Hz (same parameters used above for the transient MLR), a 8 msec duration and 2 msec rise and fall time for a repetition rate of 20 Hz, 5.6 msec duration and a 1.4 msec rise and fall time for a repetition rate of 40 Hz, and a 4 msec duration and 1 msec rise and fall for a repetition rate of 80 Hz (same parameters used above for the transient ABR).

ASSRs are elicited traditionally by modulated tones. However, the use of AM tones, *per se*, was deemed inappropriate for this endeavor. Amplitude modulated tones at a frequency of 40 Hz (with a recording window of at least 25 msec duration) results in a strong representation of the modulation frequency in the underlying MLR waveform. The effective rise time at 40 Hz is 6 msec which approximates the effective parameters of TBs for the MLR (Beiter & Hogan, 1973; Vivion et al., 1980; Xu et al., 1997). Thus at 40 Hz, amplitude modulated tones and TB

are similar. In addition, results in the literature and our experience have shown that these stimuli are also highly effective for 80 Hz. In contrast, for frequencies significantly less than 40 Hz, the corresponding rise time (in terms of AM envelope) would not compare favorably with effective TBs for eliciting corresponding obligatory AEPs. An effective rise time for a recordable LLR is 20 msec or (preferably) less (cf. Subsection 3.5.1.3.), and for full-power integration appears to require only about 50 msec at most (Davis, 1976; Müller, 1973; Hall, 2006). Therefore, it seemed most appropriate to use repeated TBs as first used for the 40-Hz ASSR and later used for the 80 Hz, and because TBs are known to be highly effective for recording obligatory AEPs. In addition, basic theory and confirmation via spectrum analyses of such stimuli suggest that frequency specificity does not suffer substantially from the use of sinusoidal pulses, especially when compared with popular ASSR stimulus modes as combined AM and FM. On the other hand, the pulsatile stimulus presented in trains, as integral to ASSR analysis, demonstrates both a strong fundamental and rich overtones in the long-term spectrum.

Stimuli for transient and steady-state recordings were presented to the right ear of each subject through an insert earphone (ER-3A) at suprathreshold levels of 70 dB SPL. Pure tones (i.e. unmodulated carriers) of 1 kHz were used for calibration, taking a peak-equivalent approach. The ER-3A output was calibrated using a Zwislocki coupler mounted on Kemar. The acoustic output was sampled by a B&K 4134 microphone and read by a B&K 2231 sound-level meter.

4.3.2 Recordings

Silver-silver chloride electrodes were affixed at vertex (tied, non-inverting input), ipsilateral and contralateral mastoid (inverting inputs) and nasion (ground of the recording amplifiers) with inter-

electrode impedances of less than 5 kilohms at 30 Hz (Grass Instruments EC2). Separate parameters were chosen to enable the recordings of each transient AEP. The bioelectrical activity of the ABR was amplified using a gain of 100 K with a band-pass filter of 100-3000 Hz. With an acquisition rate of 20 per sec, 4096 sweeps were averaged to obtain a reproducible ABR. The MLR was amplified using a gain of 100 K with a band-pass filter of 10-1500 Hz. With an acquisition rate of 10 per sec, 2048 sweeps were averaged to obtain a reproducible MLR. The LLR was amplified using a gain of 50 K with a band-pass filter of 0.4-30 Hz. With an acquisition rate of 0.63 per sec, 512 sweeps were averaged to obtain a reproducible LLR. All settings were executed under computer control and, together with the methods above, avoided disturbing the subject's state throughout the recording (cf. Subsections 5.11, 5.12, 5.13; parameters reviewed by Hall, 1992).

The same electrode montage and type of recording electrodes were used for ASSR as for transient AEP testing. All steady-state testing was accomplished using a recording amplifier gain of 100 K. For repetition rates of 0.75 to 20 Hz, a band-pass filter of 0.4-100 Hz was used, and for 40 and 80 Hz, 100-3000 Hz was employed (half-voltage bandwidth, RC response in either case). In order to eliminate high levels of noise during recording, an entire sweep (see below) was rejected if it contained any potential with amplitudes greater than $\pm$50 μV within 50-ms window. For repetition rates of 40 and 80 Hz, the evoked response test system used an analog-to-digital conversation rate of 20 kHz, which was down-sampled to 1 kHz for a final spectral resolution of 0.9765 Hz. With an acquisition rate of 1024 points per second (1 sweep), robust responses with relatively low noise, i.e., threshold search, is readily achieved by 160 sweeps (often less in the general population). For the ASSR software, for lower repetition rates, progressively lower sampling rates were required as repetition rate was decreased below 40 Hz.

Therefore, sampling rates and acquisition windows realized were as follows: at 0.75, 1.25 and 2.5 Hz--100 Hz, 10.24 sec; 5 Hz--200 Hz, 5.12 sec; 10 Hz--400 Hz, 2.56 sec, 20 Hz--800Hz, 1.28 sec; 40 and 80 Hz--1000Hz, 1.024 sec. Time-ensemble averaging was incorporated (i.e. quasi-continuous stimulation while repeating the acquisition window and effectively averaging across windows) to enhance the SNR prior to spectrum analysis. The maximum number of sweeps averaged was varied such that the total acquisition time was approximately four minutes, in the combined interests of reasonably good SNRs but manageable durations of experiments, given the number of conditions tested.

In addition, from clinical experience in the temporal analyses of evoked potentials, it is possible with the use of filtering, to be given a false impression of a reproducible peak component where none actually exists. Thus, to test in the spectral analyses of steady-state responses whether anything comparable to this event would occur, no-stimulus control trials were carried out to serve as a baseline from which to judge the amplitude of the noise in the ASSR stimulus evoked response.

4.3.3 Individual and group data analysis

4.3.3.1 Temporal analysis for transient-EPs

For each subject, AEPs were analyzed for the presence of components (i.e., wave V for the ABR, N_a-P_a for the MLR, and P_1-N_1-P_2 for the LLR). Grand averages for each AEP were computed. Peak latencies were measured from the midpoint of each wave, whereas amplitude was computed from the baseline to the peak or trough of that wave.

4.3.3.2 Spectral analysis for quasi-steady-state

Spectral analyses of ASSRs routinely provided by SmartASSR for the 40 and 80 Hz conditions proved neither to be adequate or adaptable for the lower rates. Consequently, thanks to data file compatibility between the SmartASSR and SmartEP programs, the spectral analysis routine of the latter proved useful. Still, data analyses, per se, for purposes here, required further adaptations made possible by ASCII file dumps provided by the software and importing these files to spreadsheet programs (Microsoft's Excel and Polysoft's PSI-Plot).

At the outset of the study, the manufacturer (Intelligent Hearing Systems; Miami, FL) was asked to provide alternative subroutines to permit access to ASSR type stimulus control and analysis using repetition (modulation) rates (frequencies) less than 40 Hz (40 Hz and 80 Hz being native rates for their commercialized software-firmware-hardware package, called Smart ASSR). The manufacturer developed appropriate control files, as well as provided a modification of the recording preamplifiers to bring the high-pass cut-off down to 0.4 Hz (rather than their usual low frequency limit of 1 Hz, half-voltage cut-off; RC response). The sequence of control files requested was to provide modulation frequencies from 20 Hz down in octaves to 0.625 Hz. The latter rate falls substantially below those accepted as capable of eliciting robust LLRs, that is, rates < 1.1 Hz. Results of preliminary trials and bench-top testing of the instrumentation demonstrated overall efficacy of the "low-frequency ASSR" protocols, although several "bugs" were identified and worked out of the system (e.g., extending the capture window to as long as 10 sec, rather than the native 1 sec); ensuring proper behavior of the double-buffering routine, essential to noise-floor estimation, etc.). Data acquisition and analysis was well underway when, unfortunately, the manufacturer found an error in the repetition "clock" parameter for the digital signal processer in the 0.625 Hz control file, such that the true rate was

found to be 0.75 Hz. However, this difference was deemed minor for purposes of this investigation, as 0.75 Hz is still well below 1.1 Hz. Similarly, the octave modulation frequency, 1.5 Hz, is not much different than 1.25 Hz, the next specified rate. Furthermore, as the stimulus production routine is virtually free-standing (including its own clock to independently control stimulus frequency and envelope timing parameters), only the inter-stimulus interval was affected, i.e., slightly shortened in reference to the original specification. Analysis of grand averages of LLRs captured via the ASSR protocol subsequently were found to correspond well with the grand average of the LLR tested conventionally using a stimulation rate of 0.63 Hz. Hence, the comprehensiveness of the range of rates tested was not found to be compromised, namely full-filling the research-design objective to have, on the long-latency end of the range, essentially the same LLR test conditions as commonly demonstrated via conventional methods. The purpose of incorporating transient response testing, in the first place, was simply to quantify subject samples as cohorts demonstrating characteristic responses in the three major latency windows (as determined by largely conventional paradigms for testing the classical transient AEPs). Lastly, direct quantitative comparisons between transient- and ASSR-LLRs for purposes of statistical analyses directed toward hypothesis testing were not indicated by the research design. The study thus was completed using the rates of 0.75, 1.25, 2.5, 5.0, 10, 20, 40, and 80 Hz.

In conceiving this study, considering the existing steady-state-response literature, the spectral power at the fundamental, per se, was taken as the logical focus of the analyses of the amplitudes of the responses (defined below). Should the recordings and descriptive statistics subsequently demonstrate other salient spectral components, it was reasoned that these could be explored via post-hoc analyses. However, it soon became evident that power at the fundamental

would not account well for the power in the overall spectrum of all responses. Especially at the lowest repetition frequency, the fundamental actually proved difficult to detect. An overall amplitude measure of the response was thus sought. A conventional measure from acoustics that seemed to offer a reasonable basis of an approach is that of percent total harmonic distortion (THD) (Beranek, 1988). For instance, THD is specified in the performance analyses of stereo hi-fidelity amplifiers. This measure is calculated as follows:

$$\text{THD} = 100 \text{ x } \sqrt{\frac{p2^2 + p3^2 + p4^2 \cdots}{p1^2 + p2^2 + p3^2 \cdots}} \qquad \text{[Eq. 1]}$$

where p^1, p^2, p^3…are the observed sound pressures or voltages observed at frequencies F_1, F_2, F_3, etc., namely the fundamental frequency and its harmonics, wherein subscript 1 is the fundamental frequency and successive integers ≥ 2 denote the harmonics. However, in the case of the present study, the interest is the term appearing in the denominator of Eq. 1, i.e. the sum of the voltages squared, including both the fundamental and all measureable harmonics. Thus, Eq. 1 was simplified to define the measure used, dubbed "harmonic sum" (HS), computed as follows:

$$\text{HS} = \sqrt{p1^2 + p2^2 + p3^2 \cdots} \qquad \text{[Eq. 2]}$$

For spectral analyses and to compute the HS from the data generated by the software employed in this study, steady-state responses for each test condition were broken down into two plots, the 'response' which was the average of the rarefaction and condensation sweeps of the

two buffers (apropos the "split" or double-buffering employed in the signal acquisition protocol of the test system employed), and the 'noise', estimated by the difference between the two buffers. The software provided an ASCII dump of integer values from the power spectrum analysis, representing the voltage squared of the amplitudes. The HS thus was readily computed by taking the square root of the sum of these values for identified spectral components (see below). Conversions to calibrated voltages were not computed to minimize errors in data handling, as they were inconsequential to the statistical analyses (i.e. such conversion merely involves constant scaling factors across conditions or groups) and graphical analyses were presented via normalized values to a common or referent condition and group (i.e. adult awake at 0.75 Hz; see below).

For analyzing individual responses, the total response at each modulation rate was examined for spectral components that were identified to be integer multiples of the fundamental frequency. In deference to inherent limits of frequency resolution via digital analyses (e.g., binary rounding), the frequency component was scored and its amplitude taken as the peak falling ± 5% of the target frequency. The estimated background noise was then superimposed on the response spectrum to identify the components that were less than the estimated noise (i.e., having a signal-to-noise ratio < 0). These components were excluded from subsequent analyses, starting with computation of the HS.

For analyzing group data, grand averages were computed for response and noise spectra for each modulation rate. For purposes of presenting and characterizing the grand averaged response and noise spectra by group and by condition, each spectrum was normalized re the maximum power of the "adult awake" spectrum at each repetition rate. Thus, all spectra are

represented in plots wherein the ordinate is scaled in relative amplitude. In addition, all plots include the response and noise spectra superimposed to permit direct comparison.

4.3.4 Procedure

Subjects were tested in 2 recording sessions (approximately 1.5 hours each, depending on breaks) in a double-walled sound treated booth. To try and prevent attrition due to infection from the flu, allergies, or both, recording sessions, on average were 12 days apart. Pure–tone behavioral thresholds for octave frequencies between 0.25–8 kHz and a screening ABR, MLR and LLR were obtained in the initial recording session. Auditory SSRs in which subjects remained alert were obtained in the second recording session. A 3rd recording session was reserved for those adults who were also participating when ASSRs were obtained during sleep.

4.3.4.1 Pure-Tone Threshold Estimation

Pure-tone audiometry was preceded by otoscopic examination and tympanometry. All subjects had essentially clear canals with readily visualizable tympanic membrane and tympanograms within normal limits, defined by a peak pressure within ±100 daPa. In adults, hearing sensitivity was measured using the modified Hughson-Westlake procedure (Carhart & Jerger, 1959). Pure-tone thresholds were determined to within 5 dB, per standard clinical procedure (ANSI, 1996). Hearing with normal limits was defined more rigorously than by clinical practice, namely by thresholds of 15 dB HL or better for pure-tone octave frequencies between 0.25 and 8 kHz. In children, hearing sensitivity was measured using a modified ASHA screening protocol (ASHA, 1997). This procedure involved determining whether the child could hear at pure tone octave

frequencies between 0.25 and 8 kHz at a screening level of 10 dB HL in each ear, namely as both a rigorous and expedient test of these young subjects.

4.3.4.2 Transient AEPs

Transient AEPs were recorded, in addition to behavioral measures, for several reasons. First, maturation of auditory cortical function is not as well characterized in children as in adults, thus recordings were used as a reference point of what response measurements to expect in alert children and for comparison with what results are available in the literature. Measurements in adults are well established, thus recordings were used to confirm that response measurements obtained were typical of values reported in the literature. Second, transient AEPs were recorded to document overall functional integrity of the subject's neural auditory system. Given the subject recruitment base and that some individuals (although rarely) fail to produce a well defined ABR (Starr, Picton, Sininger, Hood & Berlin, 1996; Worthington & Peters, 1980), a screening test was given to verify major component waves of the ABR, MLR and the LLR were present. Third, at this stage of research and development in the potential extension of steady-state analysis across the entire evoked potential ensemble, it seemed only prudent to assure the presence of transient AEPs in the three major time ranges (LLR, MLR, and ABR) as a backdrop for the steady-state responses. Again, although most clearly documented for the ABR, there are normal-hearing individuals with negative neurologic histories who, for no explainable reason, fail to demonstrate robust AEPs. While not imposing exclusion criteria, per se, recording the transient AEPs at least allows the opportunity to evaluate the potential for outliers in the data set in post-hoc analysis and thereby to distinguish between failures to demonstrate a detectable ASSR component or poor (corresponding) AEP output overall.

Because LLR and MLR waveform morphology changes with level of consciousness--from wakefulness into light and then into deeper stages of natural sleep--the sequence of transient AEPs testing was not randomized. During LLR and MLR testing all subjects were instructed to remain awake and alert. Subjects were seated in a lighted sound treated room and were instructed to relax and keep their eyes open. To assure alertness, the adult subject's were required to count the number of tones during each recording, the younger subjects either watched a silent cartoon or movie. During recording, electroencephalography (EEG) and eye tracking was monitored continuously to ensure no hallmarks of drowsiness or sleep were observed during testing (e.g., decrease or disappearance in electrical activity recorded from the scalp surface, very slow eye movement or cease of eye blinking). During ABR testing the light in the sound treated room was turned off and all subjects were encouraged to sleep.

4.3.4.3 Steady-state AEPs

For the main parts of the study, subjects (adults and children) were instructed to remain awake and alert during testing. Subjects either watched a silent cartoon or movie in order to hold their attention. As with transient AEP recordings, EEG and eye tracking was monitored continuously to ensure no hallmarks of drowsiness or sleep were observed during testing. The insert earphone was kept in place without removal or repositioning throughout ASSR stimulus and no-stimulus testing.

Subjects that returned for the third recording session were instructed to remain awake while the LLR and the ASSR with a repetition rate at 40 Hz was repeated for long-term test-retest reliability. Subjects were then asked to relax and let themselves naturally fall asleep during testing (i.e. in a comfortable, semi-reclined lounge chair). Auditory SSR testing consisted of four repetition rates; half the subjects were randomly assigned to test at rates 0.75, 2.5, 10, and

80 Hz, while the other half were tested at rates of 1.25, 5, 20, and 40 Hz. The insert earphone was kept in place without removal or repositioning throughout the recording session. All subjects reported knowingly falling into a light sleep during testing.

4.3.5 Sequence of Testing

Subjects were tested in 2 recording sessions (approximately 1.5 hours each), on average 12 days apart.

1. The 1st session consisted of:
    a. Otoscopic and tympanometric examination.
    b. Pure-tone thresholds for octave frequencies between 0.25 – 8 kHz.
    c. Transient AEP testing (i.e., LLR, MLR and ABR).
2. The 2nd session consisted of:
    a. Otoscopic and tympanometric examination.
    b. ASSR testing of eight repetition rates.
    c. ASSR test-retest at 0.75 Hz.
    d. ASSR no-stimulus control conditions with repetition rates at 0.75 and 10 Hz.
3. The 3rd session for adults, who participated in the sleep portion consisted of:
    a. Otoscopic and tympanometric examination.
    b. Test-retest for the LLR and ASSR with a repetition rate at 40 Hz while awake.
    c. ASSR testing of four repetition rates.

4.4 STATISTICAL ANALYSIS

4.4.1 Type of Study

The study was a mixed model design, which permitted between subject comparisons in separate age groups (i.e., children and adults), within subject comparisons in the same age group under two different conditions (i.e., awake and asleep), and also examination of interaction effects. Comparisons were of amplitude measures across repetition rate. The within subject design was used to control inter-subject differences by having participants serve as their own control, which increased the sensitivity of the analysis to the effects of the independent variable.

4.4.2 Power Analysis

A target sample size of 20 participants per group, i.e., 20 adults and 20 children, was set based on the power analyses described below. Two power analyses were carried out considering the group by repetition rate interaction, and the post hoc comparisons of group means at the five lowest repetition rates. The first power analysis focused on the group by repetition rate interaction in the two-way mixed model ANOVA which was considered the effect of primary interest. A medium effect size (Cohen, 1988, f = .25) was posited because of the lack of similar studies in the literature from which an effect size could be estimated. Given a 0.05 significance level, a medium effect, and a moderate (r =.4) average correlation across conditions, a sample of 15 would be required to achieve a power of 80%.

The second power analysis focused on the post hoc comparisons of group means at five repetition rates (i.e., 0.75, 1.25, 2.5, 5 and 10 Hz, see below). Since the Bonferroni correction was planned, and it is predicted based on the LLR literature that N_1P_2 amplitude will be greater

for adults than for children (cf. Subsection 4.1.3; Martin et al., 1988); a one-tailed significance of .01 was used in this analysis. It was considered that more degrees of freedom would be available for the post-hoc analysis than for the interaction effect in the ANOVA. The approximate degrees of freedom applied in the power analysis were based on the pooling between- and within-subject error terms and corresponding degrees of freedom. Given the design of the present study (2 levels of the between-subjects factor and 5 levels of the within-subjects factor), 95 (i.e., 5n – 5) degrees of freedom would be available for the post hoc analysis. Based on previous research, a large between-groups difference is expected at the lowest presentation rate of 0.75, but there is no basis on which to estimate effect sizes at the other four presentation rates. A target sample of 20 participants per group, given an effect size of .6 or greater (halfway between Cohen's definitions of medium [d=.5] and large [d=.8] effects), would yield a power of 70% or higher. Experimental attrition was estimated at 25%, so total recruitment and enrollment was estimated at 25 participants per group.

However, recruiting children became a real challenge in the present study. As a result, it was decided to re-evaluate the target sample size of 25 participants per group. A new power analysis was carried out based on a sample made up of 25 adults and 12 children. These analyses focused on the same two tests that were used in the original power analysis: the group by repetition interaction in the two-way ANOVA, and the post hoc tests comparing adults and children at each repetition rate. Since power analysis software and power tables as based on the assumption of equal sample sizes, the rounded average of 18 (25 and 12), was input as the common sample size. This method of handling unequal sample sizes using SPSS statistical software to compute error degrees of freedom for within-subjects effects in a two-way ANOVA with repeated measures on one of the two factors. Results with respect to the interaction showed

that given the same specifications as in the original analysis (an alpha of .05, a medium effect size, and a correlation of .4) a common sample size of 18 would yield a power of .86. Based on a one-tailed alpha of .01, as specified in the original power analysis, and a common sample size of 18, power for the post hoc analyses would equal or exceed 70% provided that an effect size of .63 or greater was obtained, justifying the revision of the pediatric sample, i.e. 12 participants.

4.4.3 Statistical Considerations

Response amplitudes were summarized using measures of central tendency and measures of variability. To analyze the data statistically, we performed a two-way analysis of variance (ANOVA) (age group by repetition rate) to test the effects of age group, repetition rate, and the interaction between these two variables on response amplitude. In other words, this analysis allowed us to test whether significant differences in response amplitude existed between the two age groups (children and adults) when responses were averaged across repetition rate, whether response amplitude for the total sample of children and adults varied significantly across repetition rates, and whether the magnitude of differences in response amplitude between children and adults changed as a function of repetition rate. A descriptive analysis was performed to identify the repetition rate(s) which evoked maximal response amplitude as a function of age. Pearson's product-moment correlation coefficients were planned to quantify the relationship of the linear trends that were identified.

Moreover, as an exploratory examination, a two-way ANOVA (subject state by repetition rate) was planned originally to test whether state of arousal (awake versus asleep) had an effect on the response amplitude of adults when stimuli were presented at different repetition rates. However, the sample sizes for each group, awake versus asleep were not equal. Thus, paired

samples t-test was made to compare the responses of adults when awake and when asleep at selected repetition rates. Since response amplitudes for modulation frequencies greater than 10 Hz can be predicted from results of previous AEP studies, a paired samples t-test was conducted to specifically compare the amplitude differences among the age and arousal groups on the repetition rates of 10 Hz and less. Furthermore, response amplitude was graphed to identify the presence of any trends. Pearson's product-moment correlation coefficients were planned to quantify the relationship of the linear trends that were identified. However, three outliers were identified in the data for adults during sleep. Because Pearson's correlation coefficient is very sensitive to outliers, especially with small sample sizes, the Spearman rank-order coefficient was calculated to quantify the proportion of the variance in responses that can be attributed to "true" variation among individuals during sleep.

5.0 RESULTS

5.1 TEMPORAL ANALYSIS

5.1.1 Analysis of transient-EP responses

5.1.1.1 Adults

The grand averages of the ABR elicited in adults are presented in Figure 11. Overlapping stimulus artifacts are shown over the first approximate 4 ms, as expected from the relatively long tone bursts employed for ABR testing but directly adapted from the ASSR protocol (i.e. 5 ms – 0.9 ms for tubal insert delay). This makes the early ABR components difficult to identify confidently, although the IV/V complex is clearly evident. The averaged latency of wave V was 6.7 msec and the amplitude value was 0.14 uV. As expected, a small asymmetry was present between the ipsilateral and contralateral group averages, with the peak of wave V being smaller on the contralateral side.

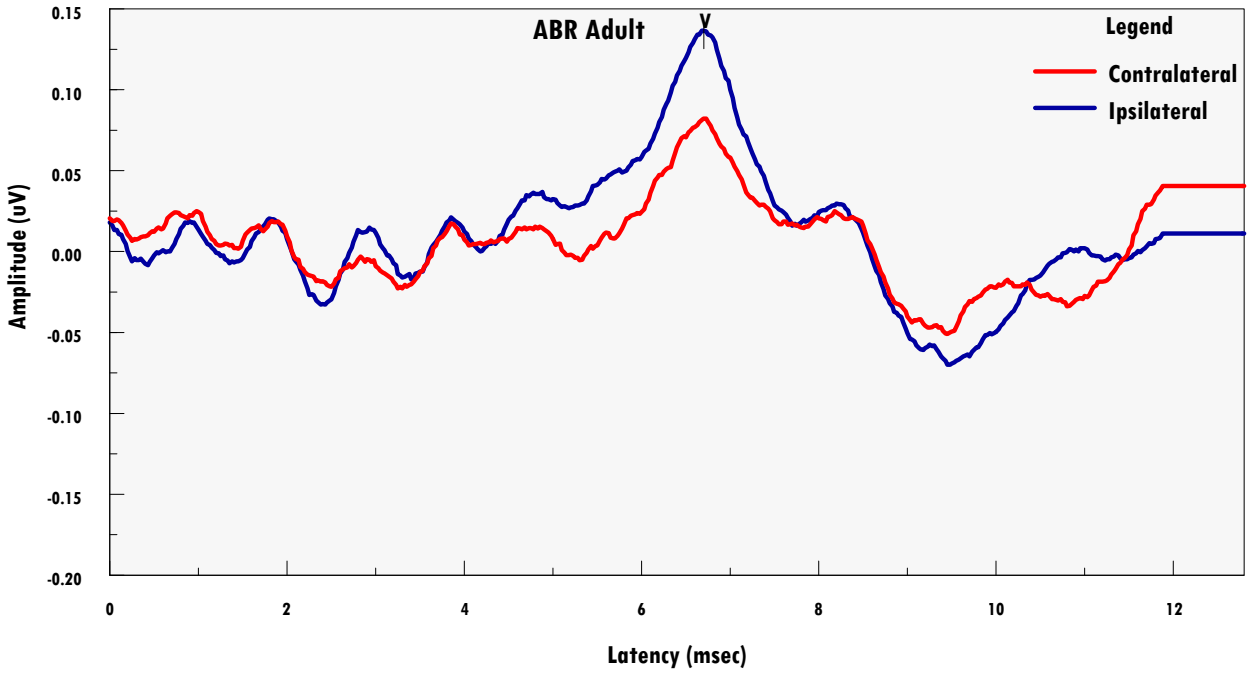


Figure 11 Grand averages ABR adult

The grand averages of the MLR elicited in adults are illustrated in Figure 12. Although overlapping stimulus artifacts are evident they are slight and a clear N_a-P_a complex could be identified. Latency values were 19 msec for N_a and 29 msec for P_a, and amplitude values were -0.25 uV for N_a and 0.56 uV for P_a. A small asymmetry was present between the contralateral and ipsilateral group averages, with the peak being smaller and the latency of P_a on the ipsilateral side being slightly shorter.

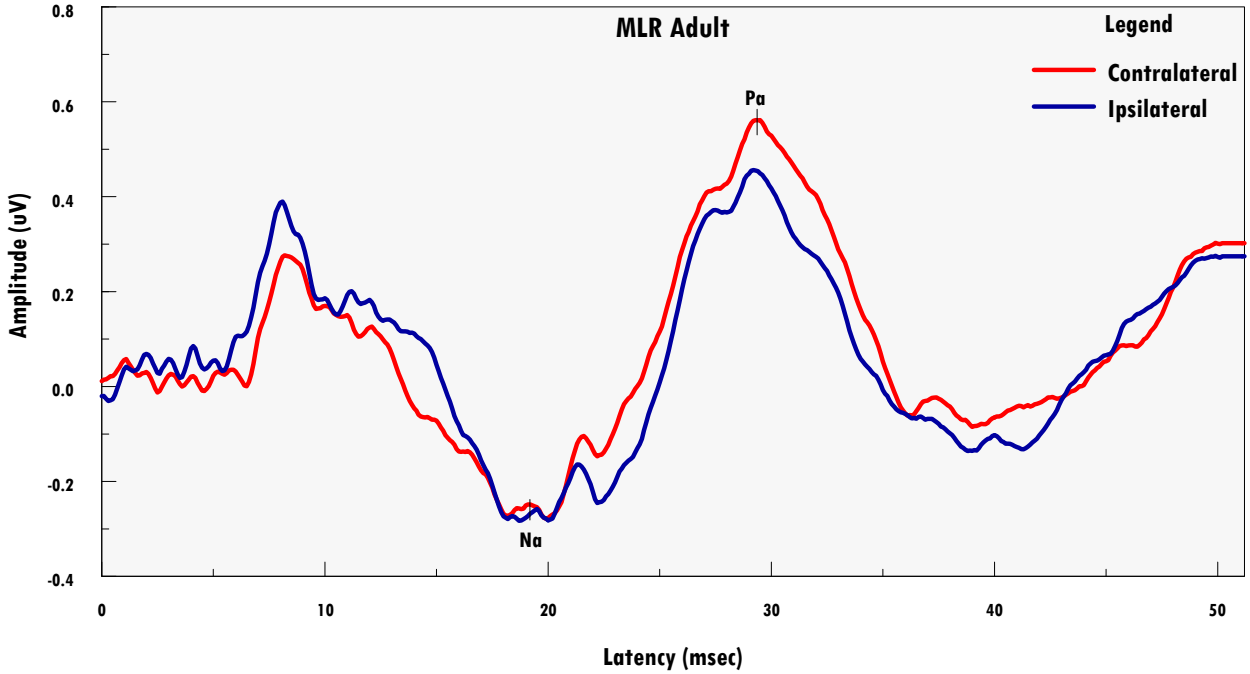


Figure 12 Grand averages MLR adult

The grand averages of the LLR elicited in adults are illustrated in Figure 13. Adults showed the classic, well-defined P_1-N_1-P_2 complex. Latency values were 35 msec for P_1, 94 msec for N_1 and 157 msec for P_2. Amplitude values were 1.3 uV for P_1, -5.2 uV for N_1 and 4.9 uV for P_2. A small asymmetry was present between the contralateral and ipsilateral group averages, with the peak of P_2 on the ipsilateral side being slightly smaller.

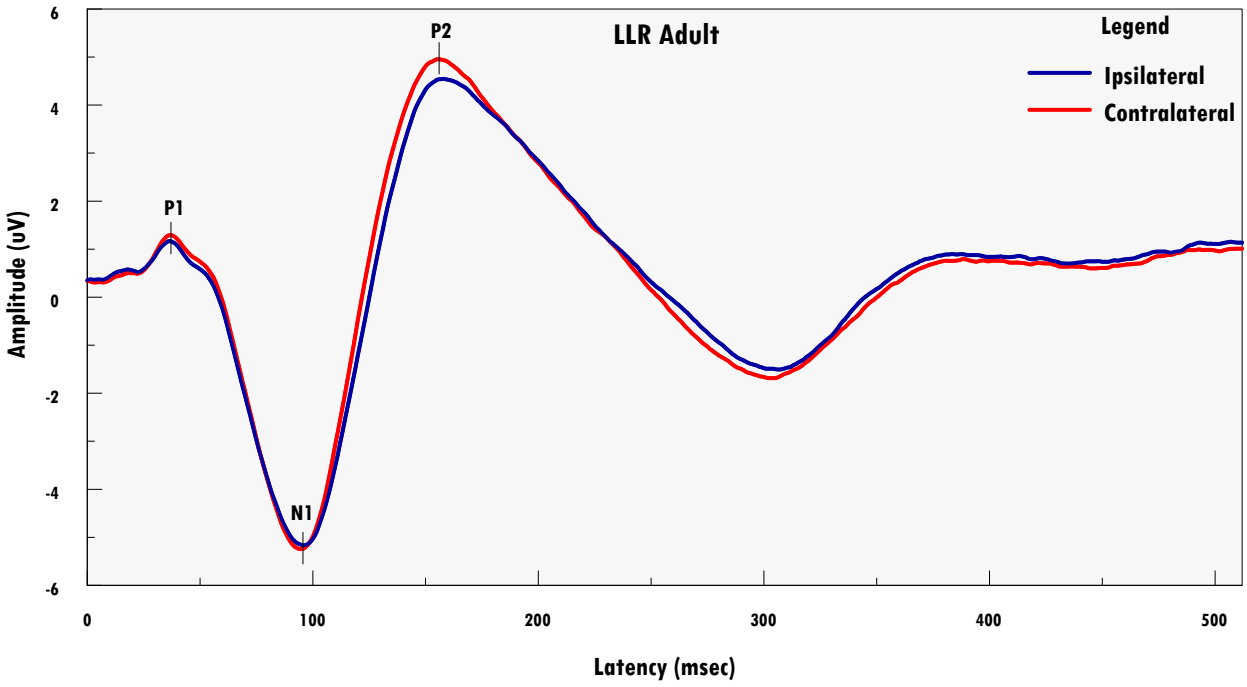


Figure 13 Grand averages LLR adult

Test-retest (between-session) results for the LLR tested in adults are displayed in Figure 14. Consistent with the original test, a small asymmetry is observed between the contralateral and ipsilateral group averages, with the peak of P_2 on the ipsilateral side being slightly smaller. Visual inspection of P_1-N_1 reveals that the amplitude and latency of the retest was nearly identical to the grand averages obtained in the original test. Although there is fairly good replicability, an examination of P_2 shows that the amplitude is higher and the latency is longer in retest compared to the grand averages obtained in the original test.

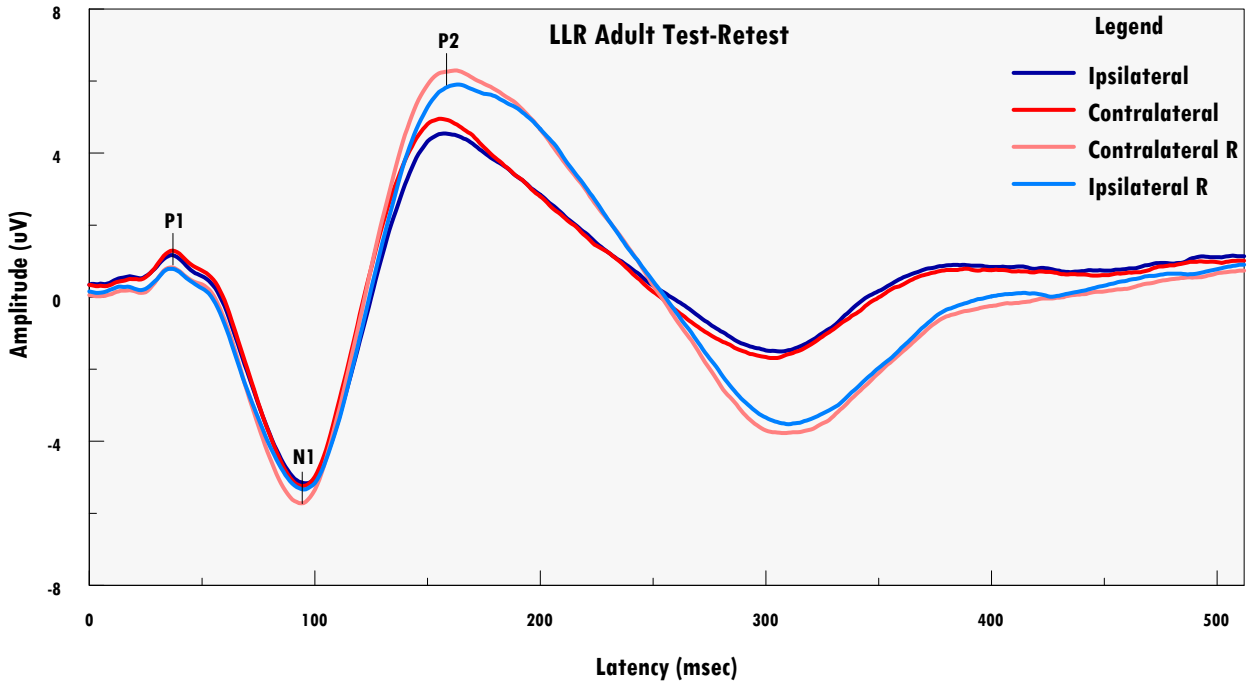


Figure 14 Between-test session reliability adults

5.1.1.2 Children

The grand averages of the ABR elicited in children are illustrated in Figure 15. Overlapping stimulus artifacts are shown, making the early ABR components difficult to identify. The grand averages for Wave V in children are rather well-defined. Averaged latency values were the same between adults and children (6.7 msec). Likewise, averaged amplitude values for both adults (0.14 uV) and children (0.19 uV) were nearly identical. Moreover, a small asymmetry was present between the contralateral and ipsilateral group averages, with the peak of Wave V on the contralateral side being slightly smaller.

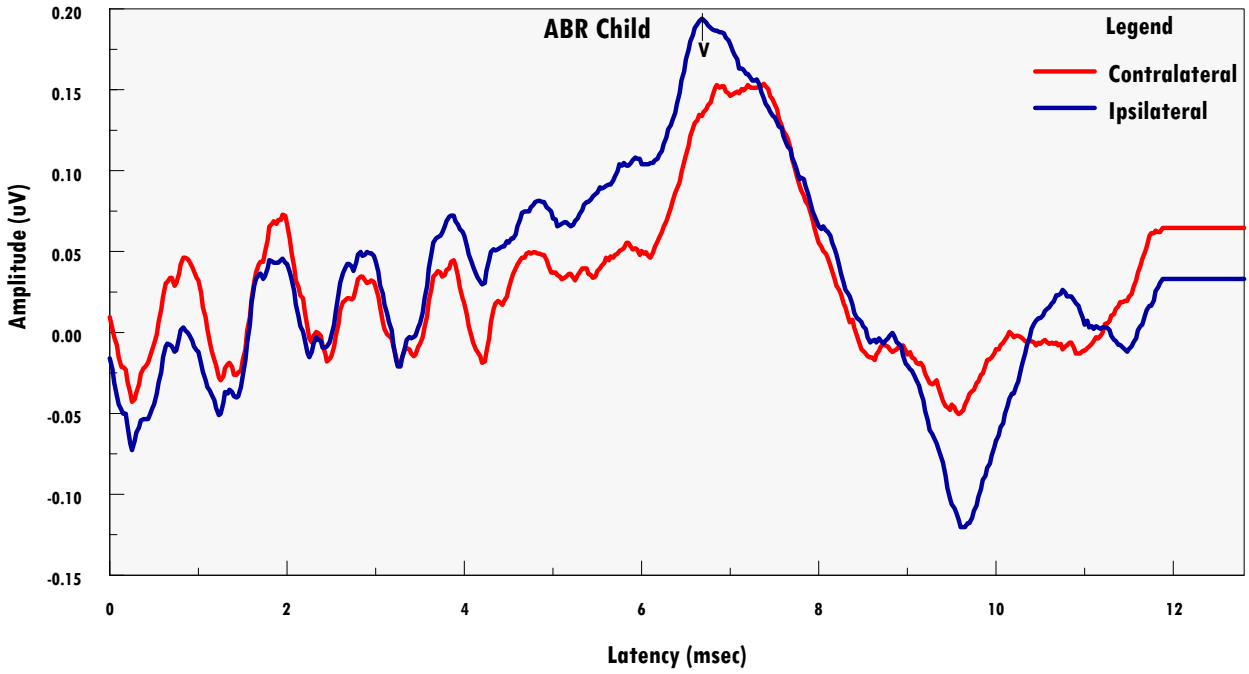


Figure 15 Grand averages ABR children

The grand averages of the MLR elicited in children are illustrated in Figure 16. The grand averages for N_a-P_a complex in children appeared less developed with somewhat more perturbations than the grand averages observed in adults. The latency values were 20 msec for N_a and 38 msec for P_a, and the amplitude values were -0.39 uV for N_a and 0.13 uV for P_a. Latency values were slightly longer and amplitude values were considerably smaller in children compared to the grand averages obtained in adults.

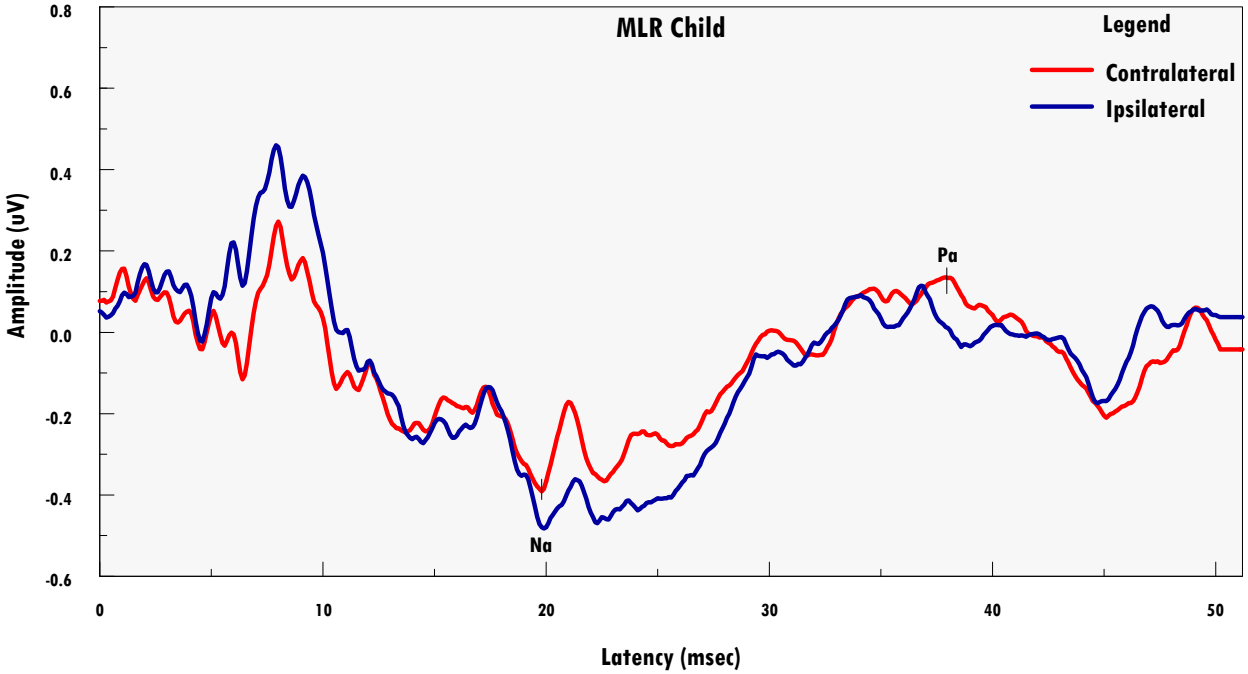


Figure 16 Grand averages MLR children

The grand averages of the LLR elicited in children are illustrated in Figure 17. The grand averages for the P_1-N_1-P_2 complex in children appeared less mature than the grand averages observed in adults. Latency values were 62 msec for P_1, 98 msec for N_1 and 146 msec for P_2. Amplitude values were 2.1 uV for P_1, 0.89 uV for N_1 and 3.7 uV for P_2. Thus, in children latency values were slightly longer for P_1 and N_1 and shorter for P_2, whereas amplitude values were larger for P_1, but smaller for N_1 and P_2 when compared to adults. A small asymmetry was present between the contralateral and ipsilateral group averages, with the peak being smaller and the latency of P_2 on the ipsilateral side being slightly longer.

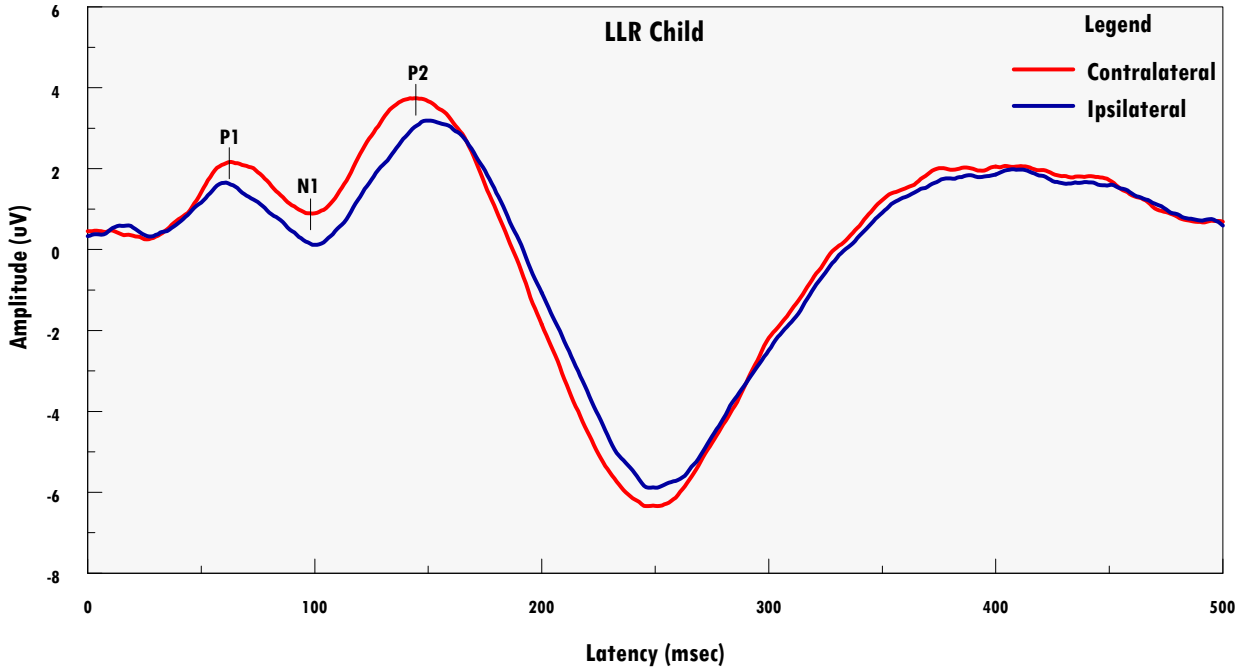


Figure 17 Grand averages LLR children

Specific Aim 1: Examine the effects of repetition (modulation) rate (frequency) on ASSR amplitude in adults and in children to (a) test between subject age-related amplitude values.

5.1.2 Analysis of quasi-steady-state responses

5.1.2.1 Adults

In order to clearly demonstrate the effect of auditory stimulation at different presentation rates on amplitude under quasi-steady-state stimulation, grand averages of the ASSR waveforms at each modulation frequency are displayed separately in Figures 18 through 21. The figures illustrate the time domain over the total response capture window (A) and for closer examination, over a shorter response capture window (B). These comparisons permit scrutiny of the effects of the

framing of the response train, ultimately submitted to spectrum analysis and similarity/differences among responses in the context of the more conventional transient response.

At the modulation frequency of 0.75 Hz, a recurrent wave complex was elicited by a pulse train corresponding to the repeated seven stimuli presented over a total response capture window of 10000 msec (Figure 18A). Closer inspection of the pulse-like train over a window of 1000 msec (B) reveals clearly the P_1-N_1-P_2 complex, ostensibly the same as that observed under the transient-response protocol, for which in fact the stimulus conditions were essentially identical. At the modulation frequencies of 1.25 and 2.5 Hz the response train consisted of 13 and 22 stimuli, respectively, over a total response capture window of 10000 msec, respectively. With the increase in modulation frequency to 1.25 Hz, there was a slight decrease in the relative amplitude of the grand averaged waveform. When the modulation frequency was increased to 2.5 Hz, the individual response components are difficult discern in the full frame (Figure 19A), but remain vivid in the shorter-window view (B). At this frequency, the amplitude of the averaged waveform was considerably decreased for all components. Although qualitatively similar, it is not clear that this waveform literally represents the LLR as the latencies of the 3-peak complex are shifted in (shorter latency) than the conventionally recorded P_1-N_1-P_2 complex.

At the modulation frequencies of 5 and 10 Hz, responses were elicited by a sinusoidal pulse train consisting of 22 stimuli over a total response capture window of 5000 and 2500 msec, respectively. Increasing the modulation frequency to 5 Hz, even in the time-expanded view (B), the averaged waveform morphology no longer bore any resemblance to the P_1-N_1-P_2, as at this frequency the inter-stimulus interval has diminished to merely 200 ms, although at least a recurrent P_1 or some variant of a P_1-N_1 complex might be technically feasible. Still, this is not

readily evident in the background noise. Conversely, a closer assessment at the onset of the response train (B), especially at 10 Hz repetition, something like the P_1-N_1-P_2 complex appears to re-emerge. Indeed, this long-latency component was interpreted as a long-latency response to the onset of the sinusoidal pulse train making up the quasi-steady stimulus. At a modulation frequency of 20 Hz, responses were elicited by a sinusoidal pulse train consisting of 22 stimuli over a total response capture window of 1250 msec. When the modulation frequency was increased to 20 Hz, the amplitude of the response actually increases substantially compared to that at 10 Hz. In addition, the waveform becomes clearly periodic, even in the background noise. The beginning of the capture window belies excitation of an over-riding mid- to-long-latency complex, again associated with the onset of the stimulus pulse train.

At modulation frequencies of 40 and 80 Hz, responses appear as virtually continuous quasi-sinusoidal signals following the repetition rate throughout the capture window of 1000 msec (Figure 21AB). When the modulation frequency was increased to 80 Hz the response amplitude decreased dramatically. A mid-to-long latency transient response remained at the beginning of the capture window, although substantially reduced (at least in part) by the upward shifted recording pass-band. Nevertheless, these 40 and 80 Hz recordings are typical of the conventionally recorded ASSRs at these modulation/repetition rates, consistent with the test protocol employed (cf. Section 4.0).

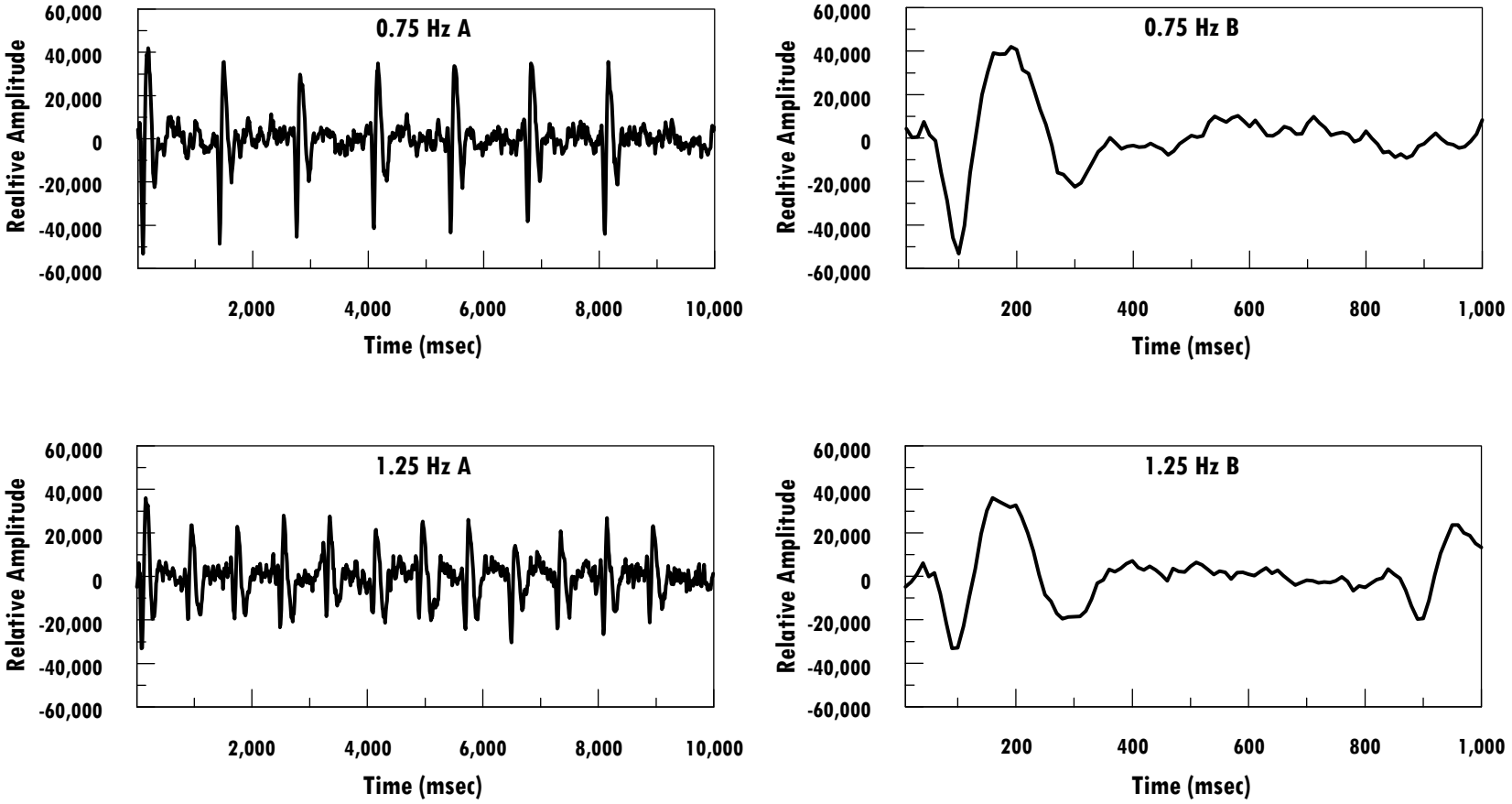


Figure 18 Grand averages at 0.75 and 1.25 Hz adults awake

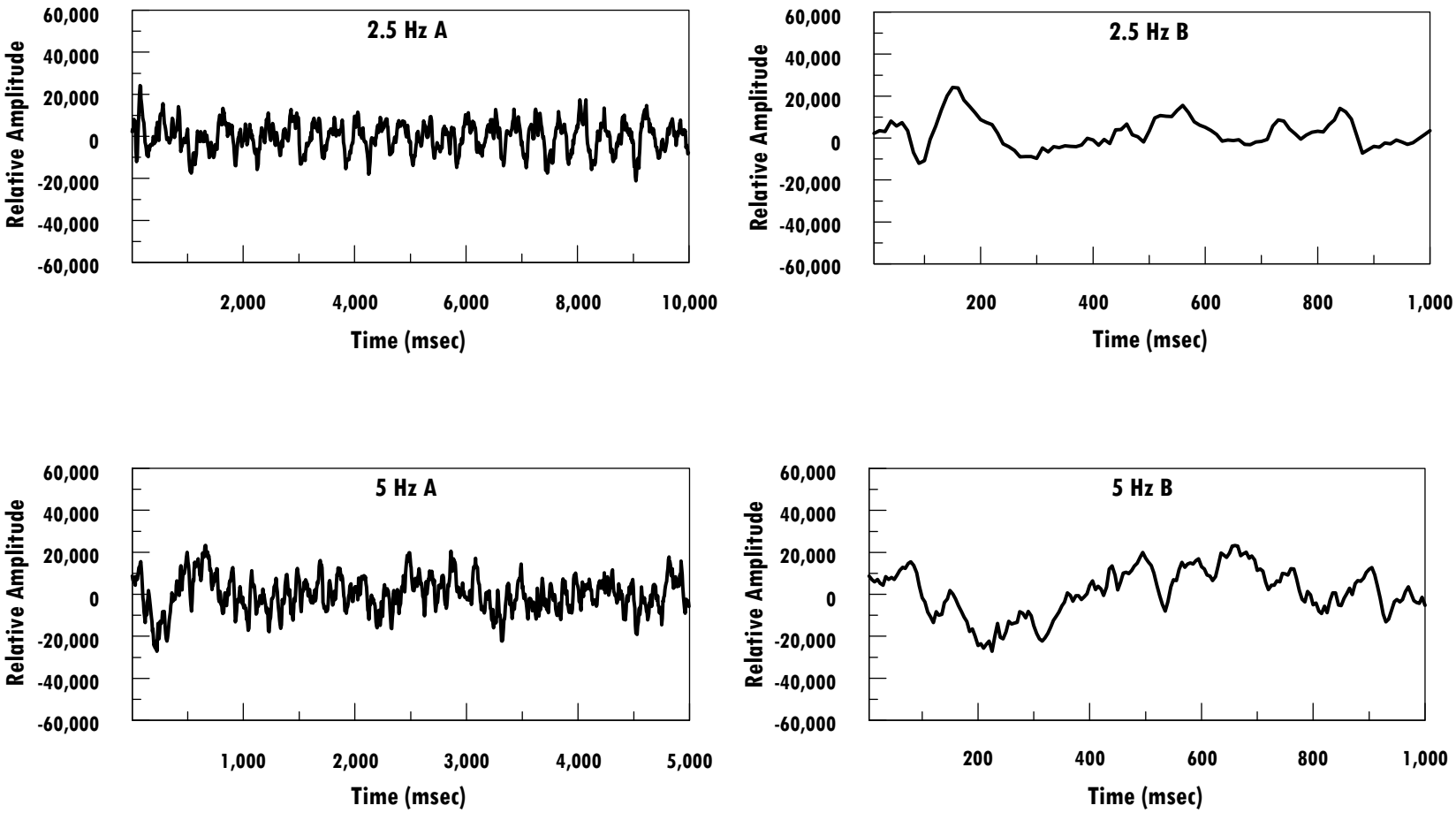


Figure 19 Grand averages at 2.5 and 5 Hz adults awake

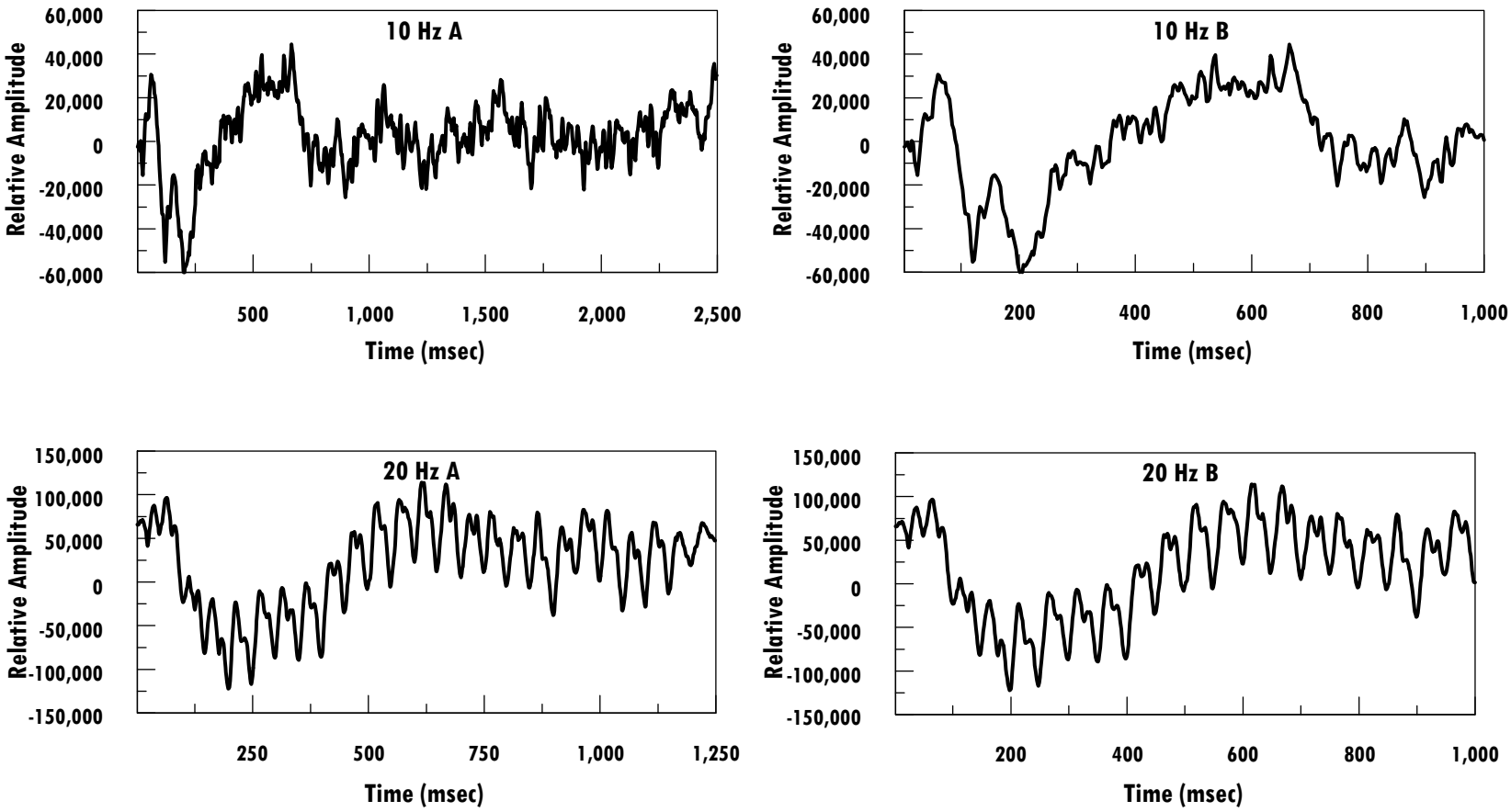


Figure 20 Grand averages at 10 and 20 Hz adults awake

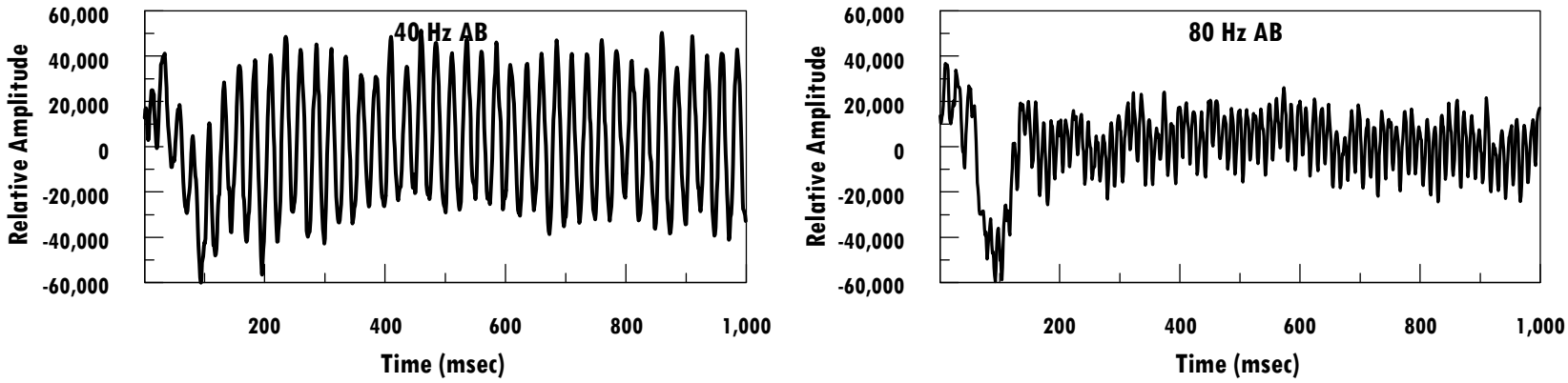


Figure 21 Grand averages at 40 and 80 Hz adults awake

5.1.2.2 Children

Grand averages of the ASSR waveforms at various modulation frequencies in children are shown in Figures 22 through 25. These figures depict the time domain over the same two response capture windows, as above, namely at each modulation frequency. For direct comparison, waveforms for both children (blue) and adults (black) have been superimposed in each of the representative figures.

At the modulation frequency of 0.75 Hz, averaged response amplitude was similar in children to the grand averages observed in adults. Scrutiny of the first 1000 msec (Figure 22B) reveals what appears to be the P_1-N_1-P_2 complex, strongly reminiscent of the conventionally-tested transient-response, but wherein the adult-pediatric differences in wave-component amplitudes are more acute at the on-set of the stimulus train. Again, in children latency values were slightly longer for P_1 and N_1 and shorter for P_2 when compared to adults. With the increase in modulation frequency to 1.25 and 2.5 Hz, the amplitude of the averaged waveform was considerably larger in children and more adult like, although different in waveform. Increasing the modulation frequency to 5 Hz, both the response train and onset response substantially increased the amplitude of the averaged response waveform, when compared to adult responses. However, at this frequency, the identity of the response (in conventional terms) is only more obscure, even in the time-expanded view (Figure 23B).

At the modulation frequencies of 10, 20 and 40 Hz the amplitude of the averaged waveform decreased when compared to adult responses. Conversely, response amplitude at 80 Hz did not change appreciably in children compared to adults. At both modulation frequencies,

the waveforms were nearly sinusoidal, with a mid-to-long latency transient response event at the beginning of the capture window, reminiscent of the response obtained in adults.

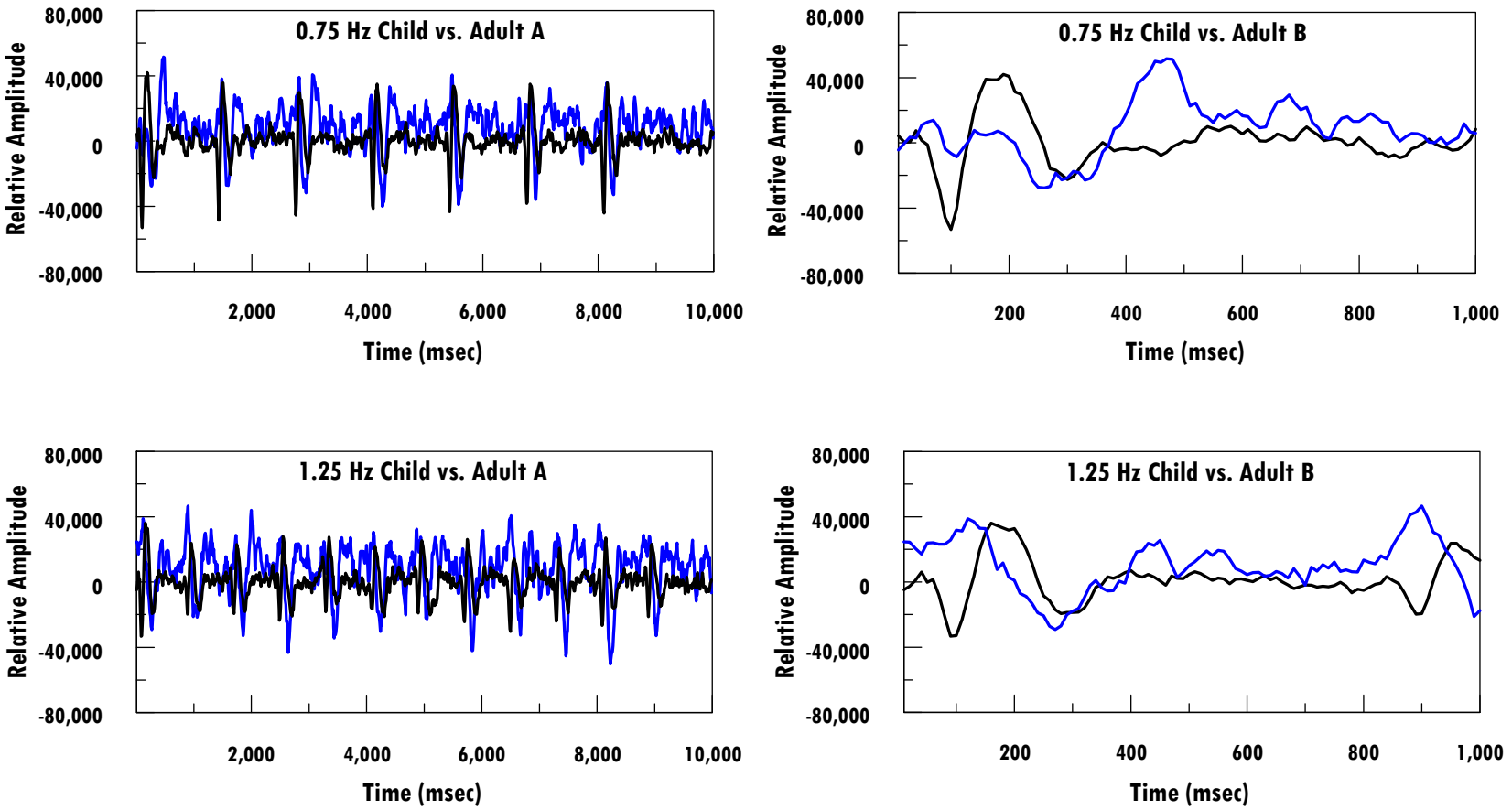


Figure 22 Grand averages at 0.75and 1.25 Hz children (blue)

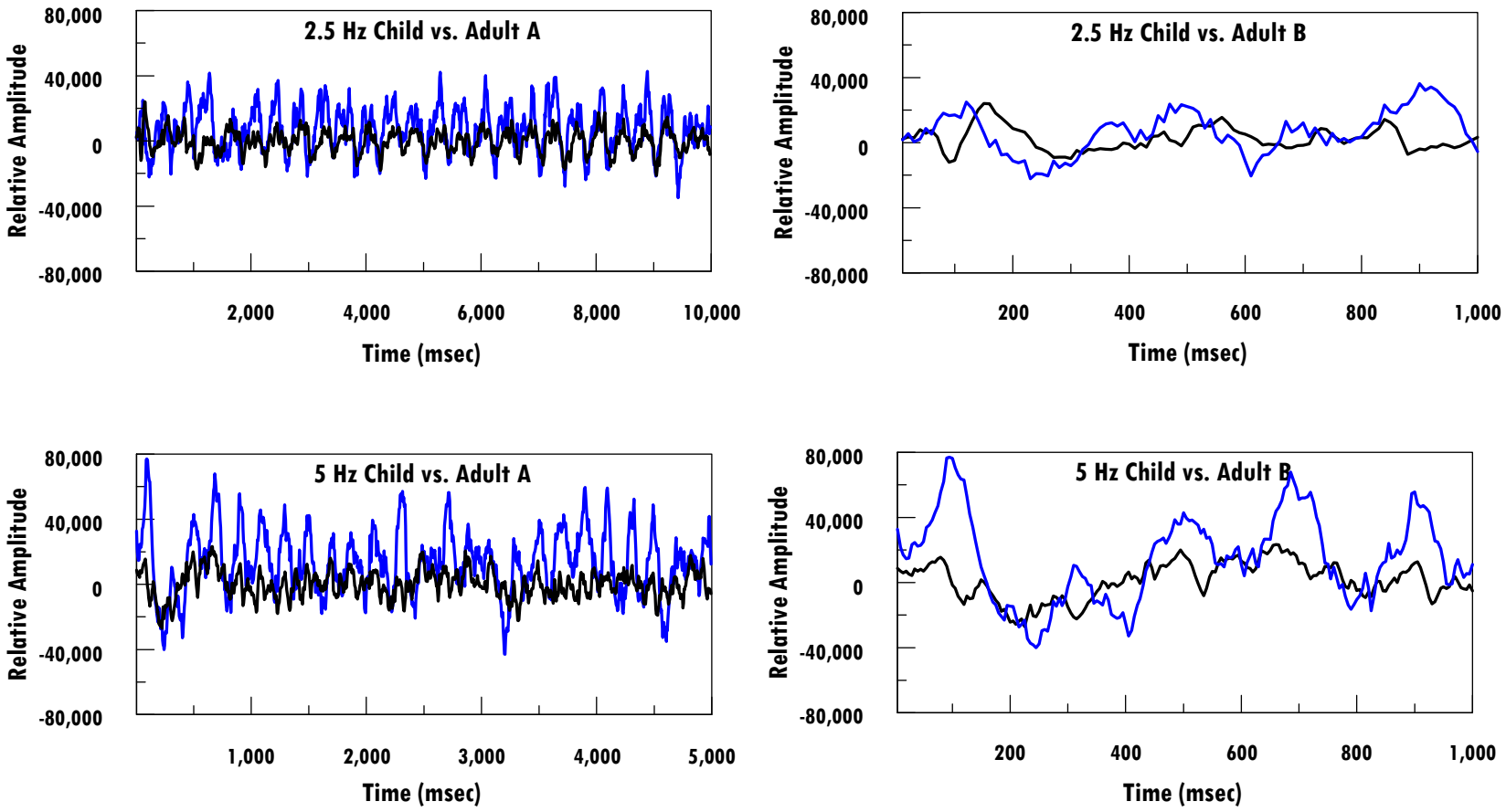


Figure 23 Grand averages at 2.5 and 5 Hz children (blue)

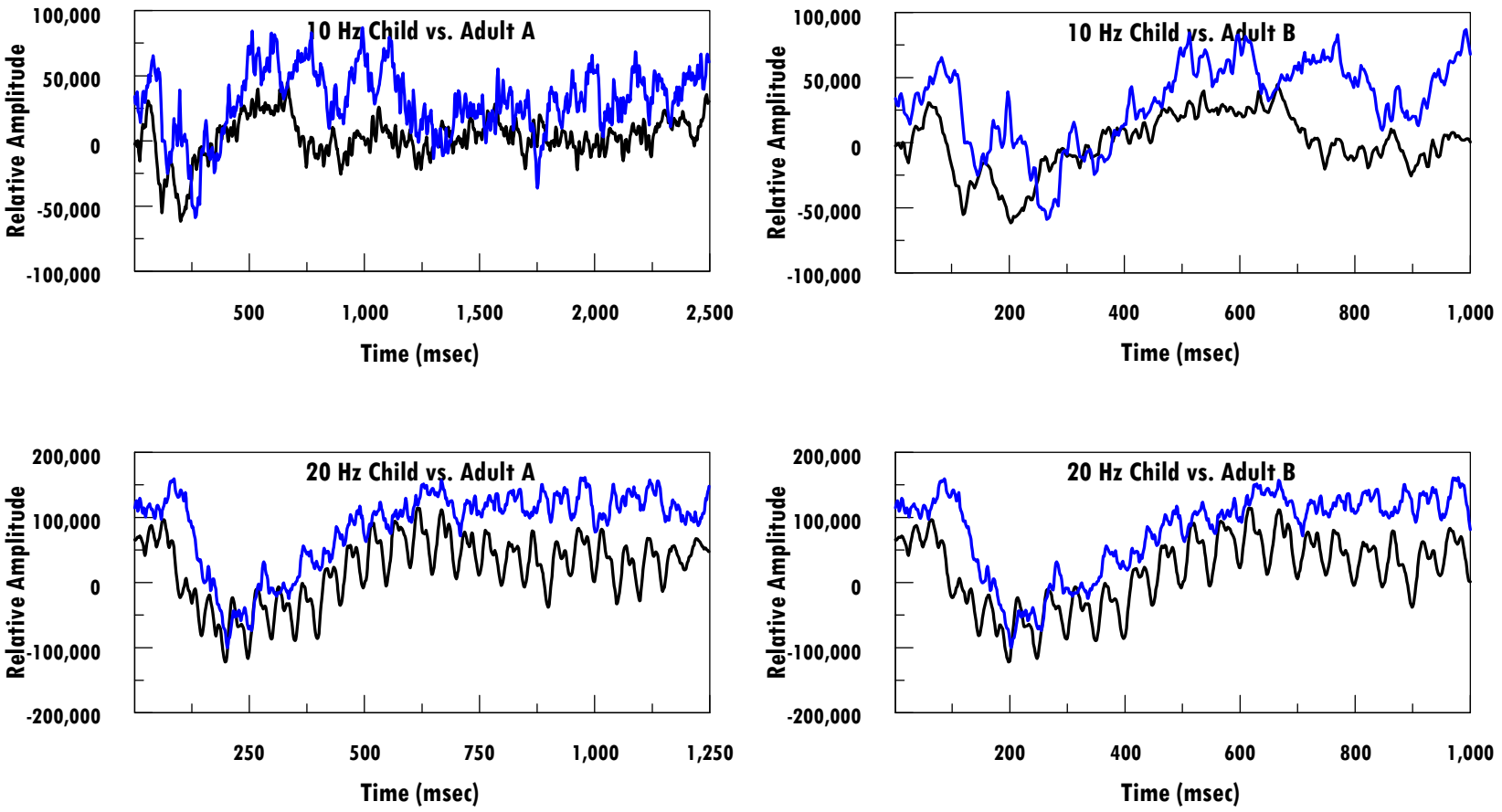


Figure 24 Grand averages at 10 and 20 Hz children (blue)

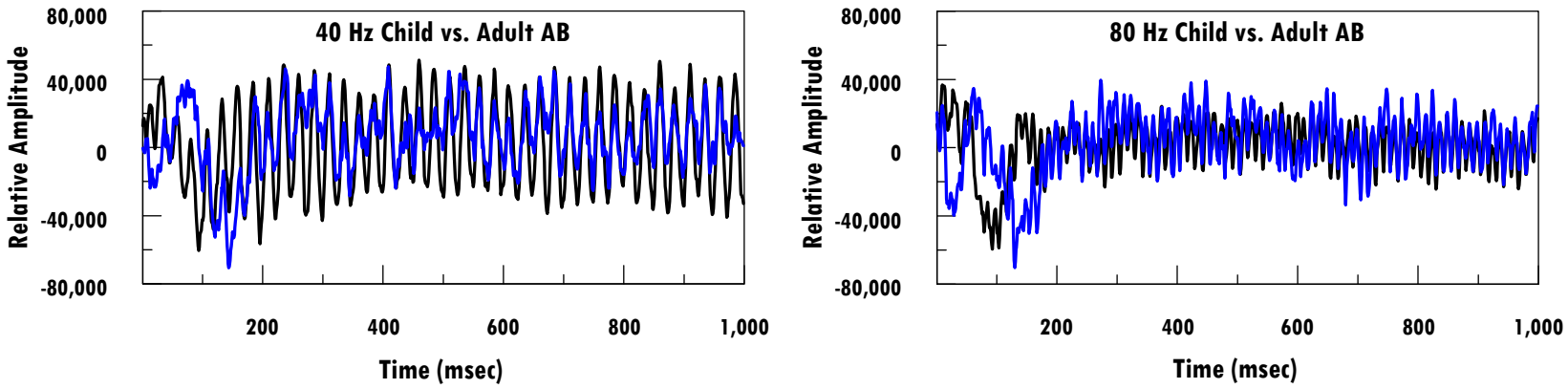


Figure 25 Grand averages at 40 and 80 Hz children (blue)

5.2 SPECTRAL ANALYSIS

5.2.1 Analysis of quasi-steady-state responses

5.2.1.1 Adults

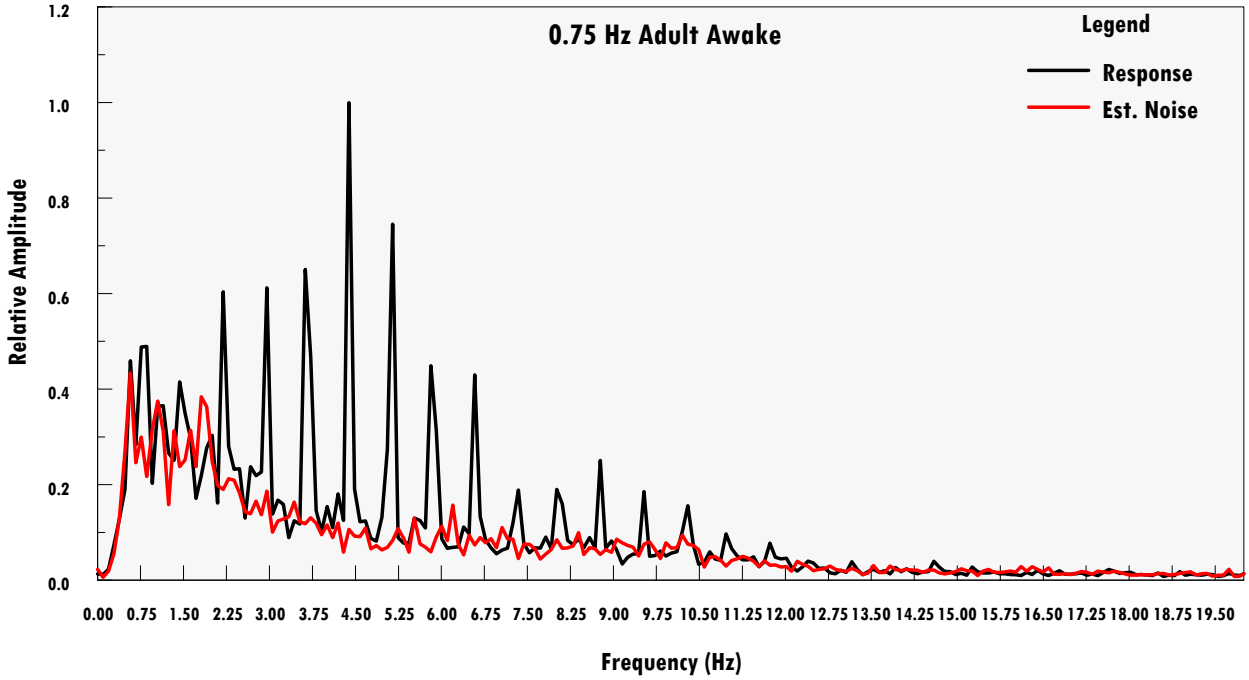
Grand averages of the ASSR power spectra at each modulation frequency are displayed separately in Figures 26 through 29. The total response and the estimated background noise have been superimposed in each of the representative figures.

When the fundamental frequency was equal to 0.75 Hz, the averaged steady-state response was represented by a series of spectral components at integer multiples of the fundamental frequency. There were 16 spectral components (black) that were identified and were considered to be equal to or greater than the estimated background noise (red). Of these 16 components, the amplitude was highest at sixth harmonic (4.5 Hz) and lowest at the 16^{th} harmonic (12 Hz) and immeasurable above. When F1=1.25 Hz, 12 spectral components that were harmonically related were identified. Of these 12 spectral components, the amplitude was highest at the fourth harmonic (5 Hz) and lowest at the 12^{th} harmonic (15 Hz) and immeasurable above.

When F1=2.5 Hz, the averaged response was represented by sharply fewer spectral harmonic components at or above the fundamental frequency. There were six spectral components that were identified and were considered to be equal to or greater than the estimated background noise. Of these six components, the amplitude was highest at the fundamental frequency (2.5 Hz) and the lowest at the seventh harmonic (17.5 Hz) and immeasurable above. Likewise, when F1=5 Hz, seven spectral components that were harmonically related were

identified. Of these seven spectral components, the amplitude was highest at the fundamental frequency (5 Hz) and the second harmonic (10 Hz), and lowest at the seventh harmonic (35 Hz) and immeasurable above. Similarly, when F1=10 Hz, six spectral components that were harmonically related were identified. Of these six spectral components, the amplitude was highest at the fundamental frequency (10 Hz) and lowest at the sixth harmonic (60 Hz) and immeasurable above.

When F1=20 Hz, the averaged steady-state response was represented by a series of spectral components at integer multiples of the fundamental frequency. There were three spectral components that were identified and were considered to be equal to or greater than the estimated background noise. Of these three spectral components, the amplitude was highest at the fundamental frequency (20 Hz) and lowest at the third harmonic (60 Hz) and immeasurable above. When F1=40 Hz, two spectral components that were harmonically related were identified. Of these two spectral components, the amplitude was dramatically higher at the fundamental frequency (40 Hz). The second harmonic, although observed, is quite small compared to the fundamental. Correspondingly, when F1=80 Hz, three spectral components that were harmonically related were identified. Of these three spectral components, the power of the spectrum was significantly higher at the fundamental frequency (80 Hz).



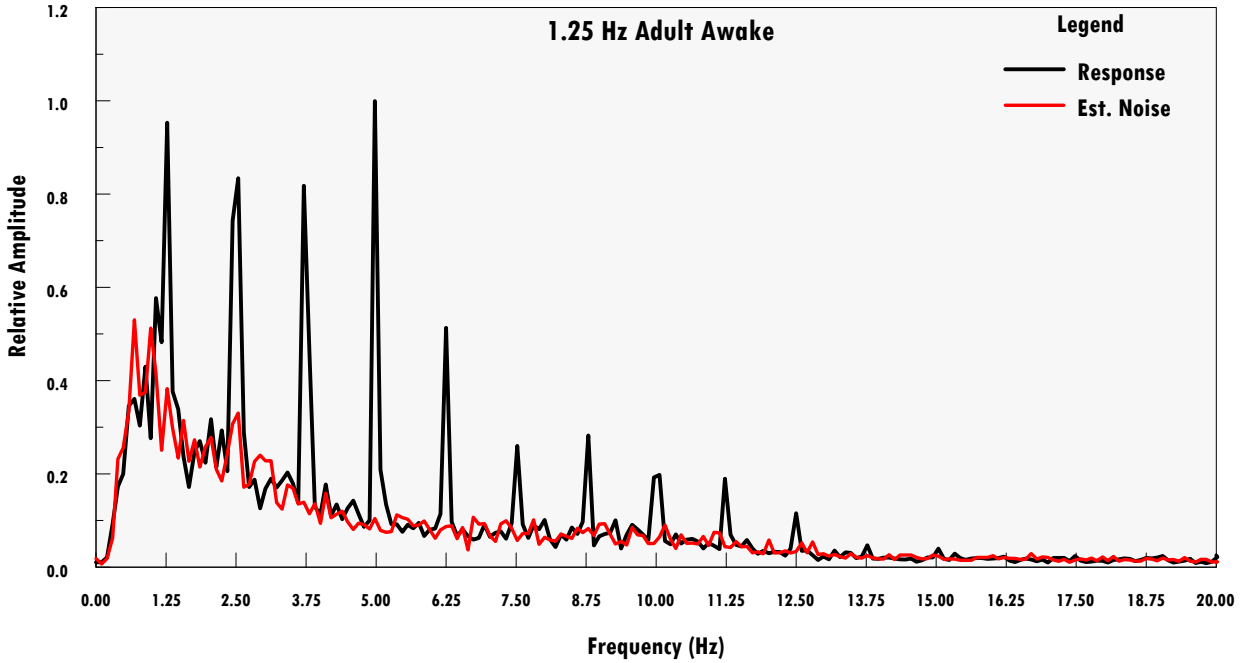
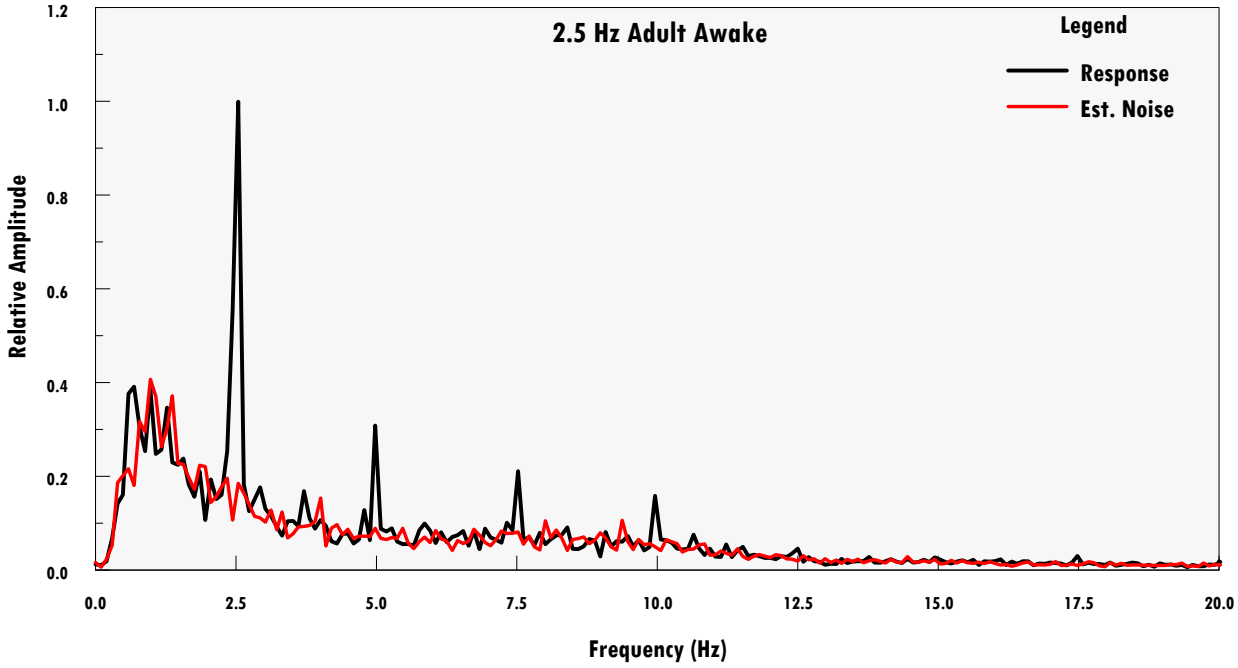


Figure 26 Grand averages at 0.75 and 1.5 Hz adults awake



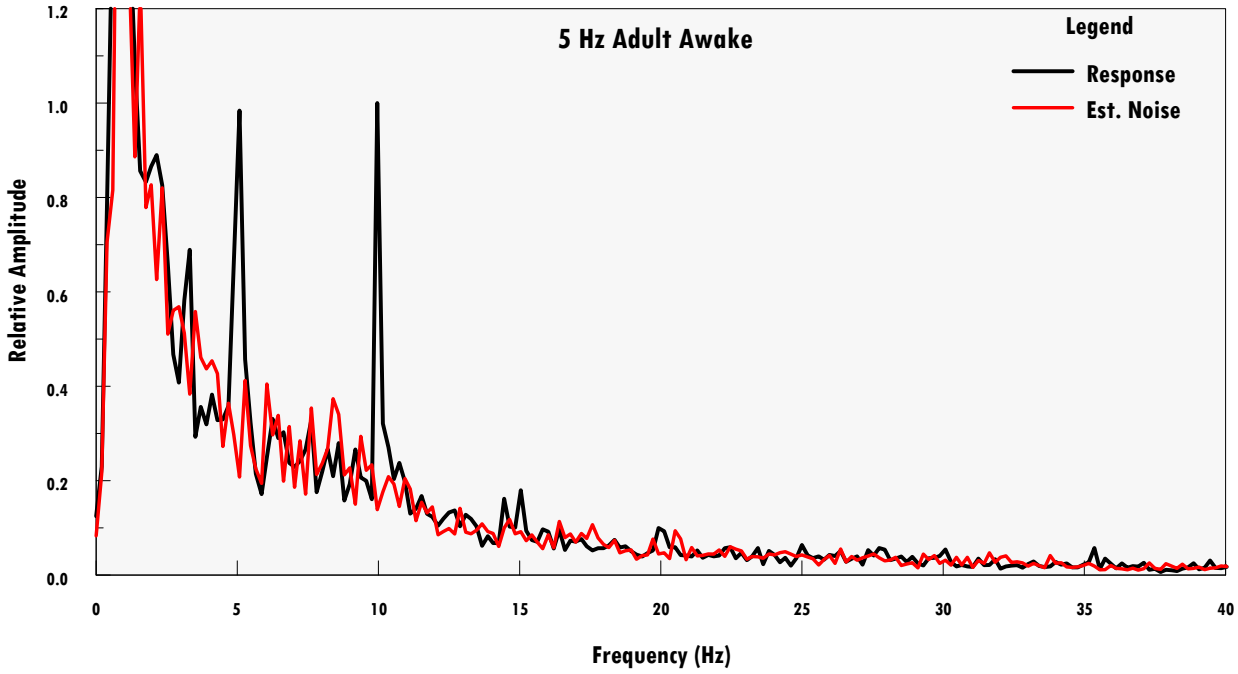
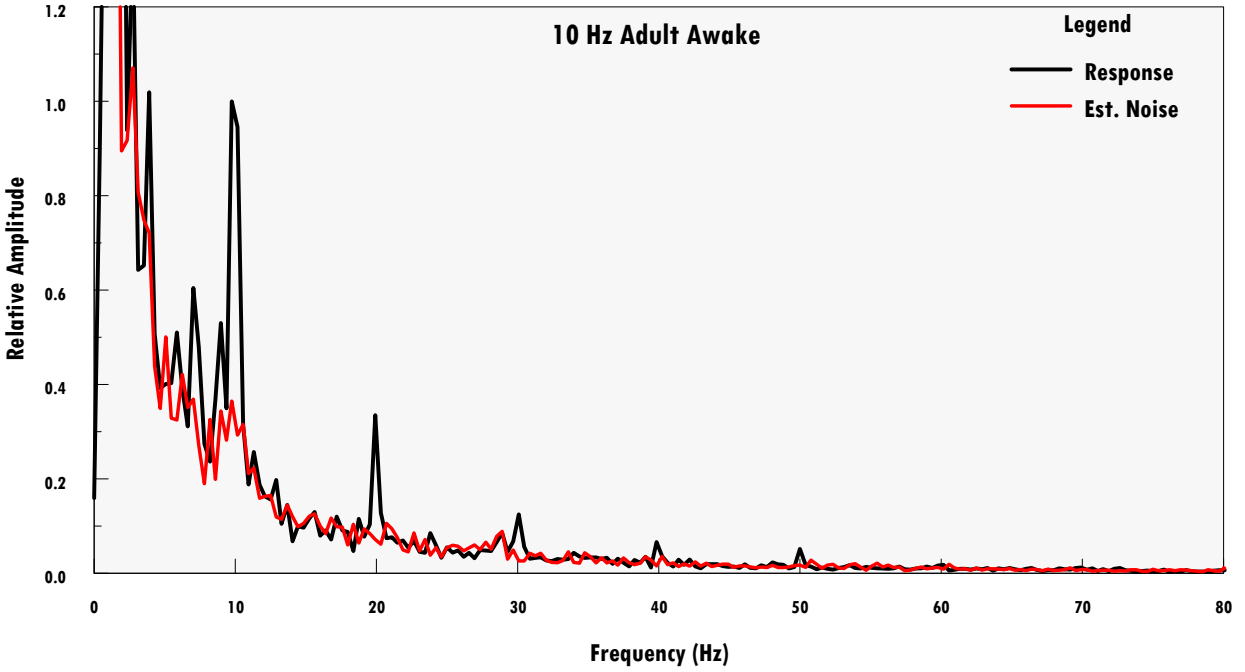


Figure 27 Grand averages at 2.5 and 5 Hz adults awake



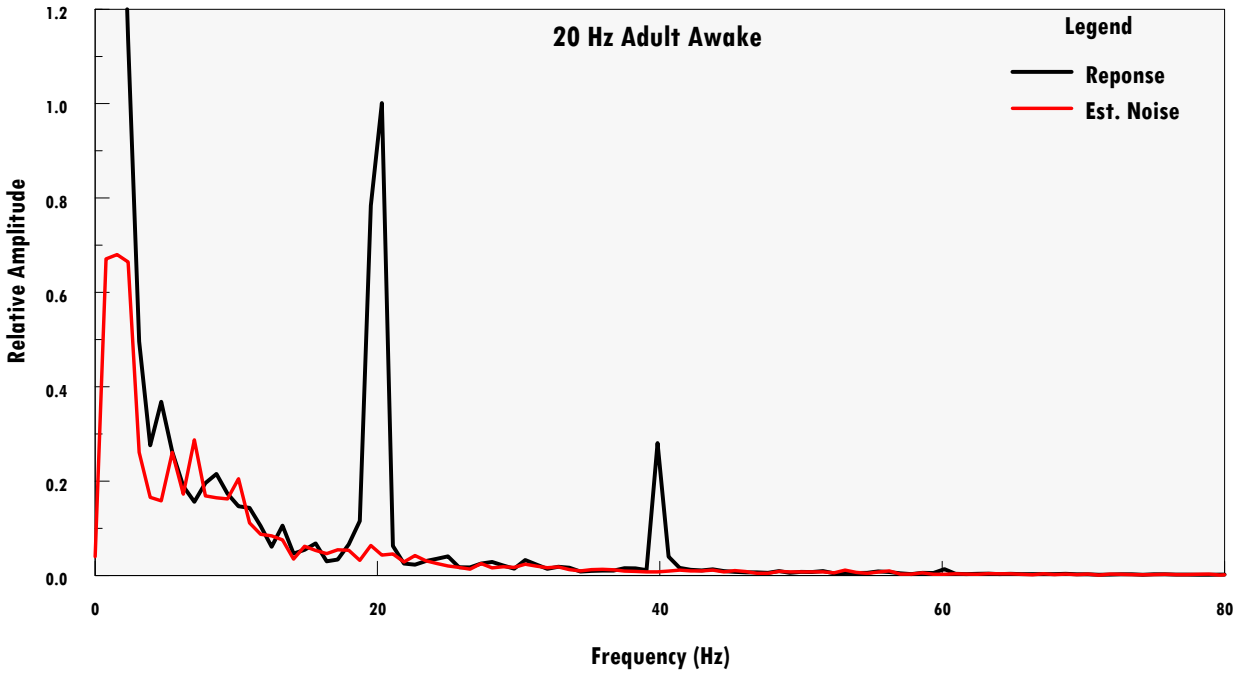
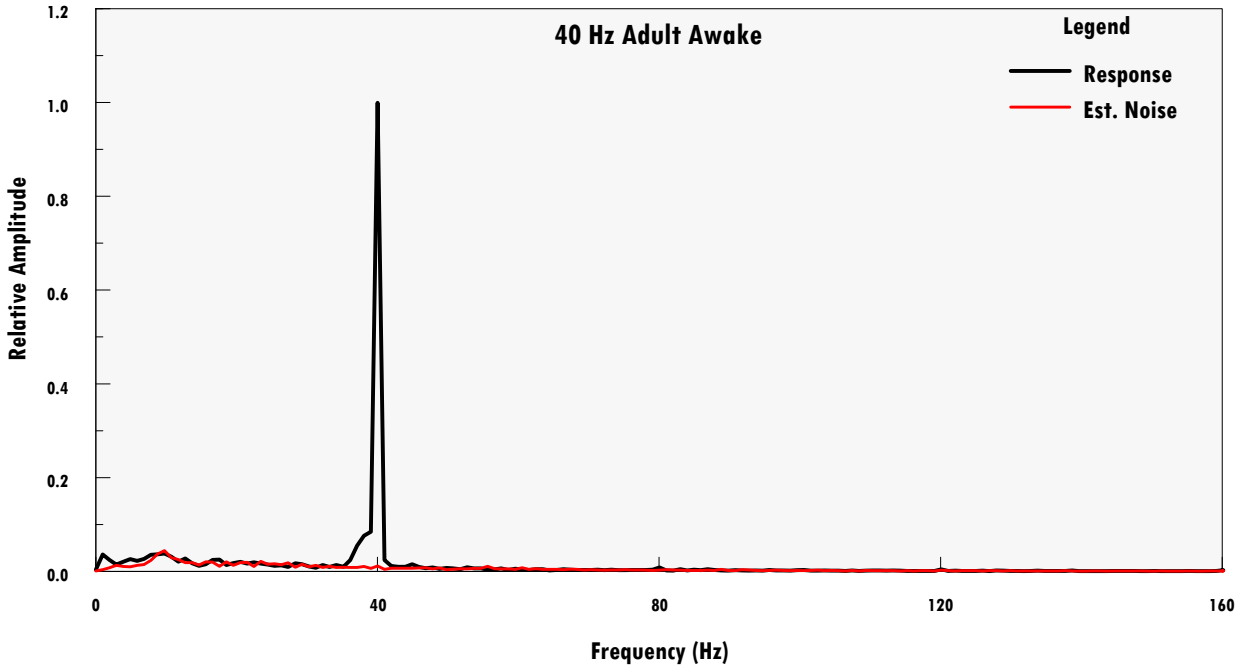


Figure 28 Grand averages at 10 and 20 Hz adults awake



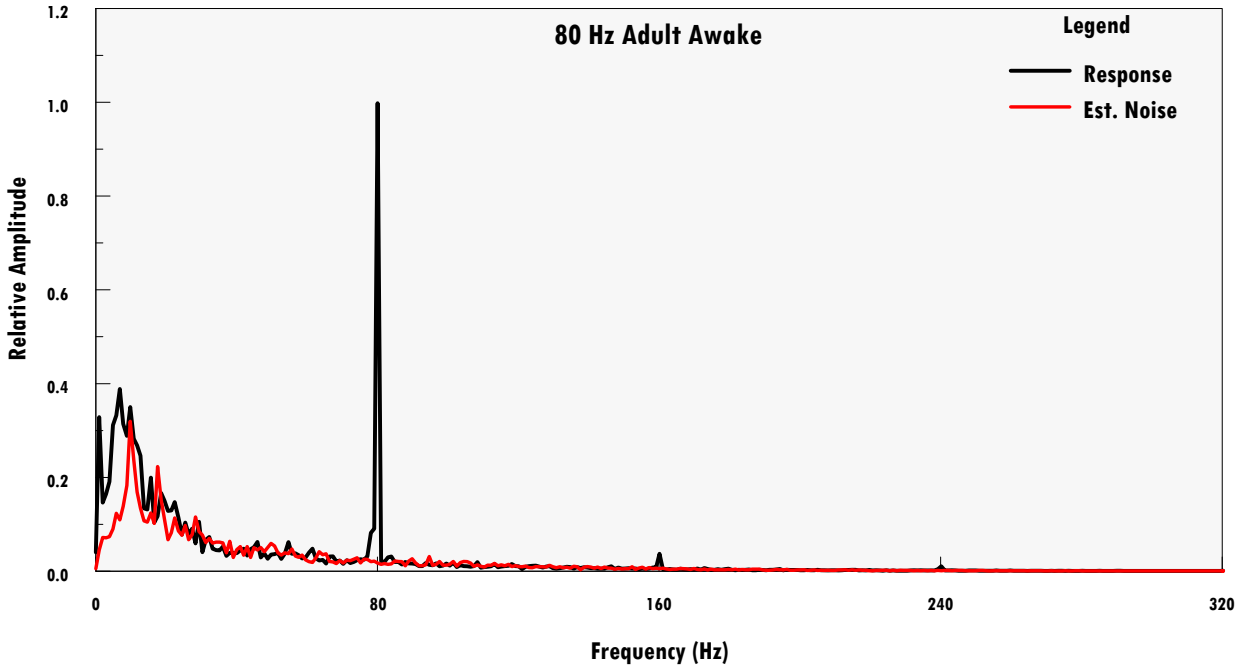


Figure 29 Grand averages at 40 and 80 Hz adults awake

A closer inspection of the first eight harmonics from each spectrum well reflects the harmonic structure of the averaged responses across modulation frequency (Figure 30). The overall structure illustrates that the number of harmonically related frequency components that were identified decreased as modulation frequency increased from 0.75 to 80 Hz. In addition, the power of the spectra was highest at the sixth harmonic at 0.75 and the fourth harmonic at 1.25 Hz, whereas, the power of the spectra was highest at the fundamental frequency at modulation frequencies from 2.5 and above.

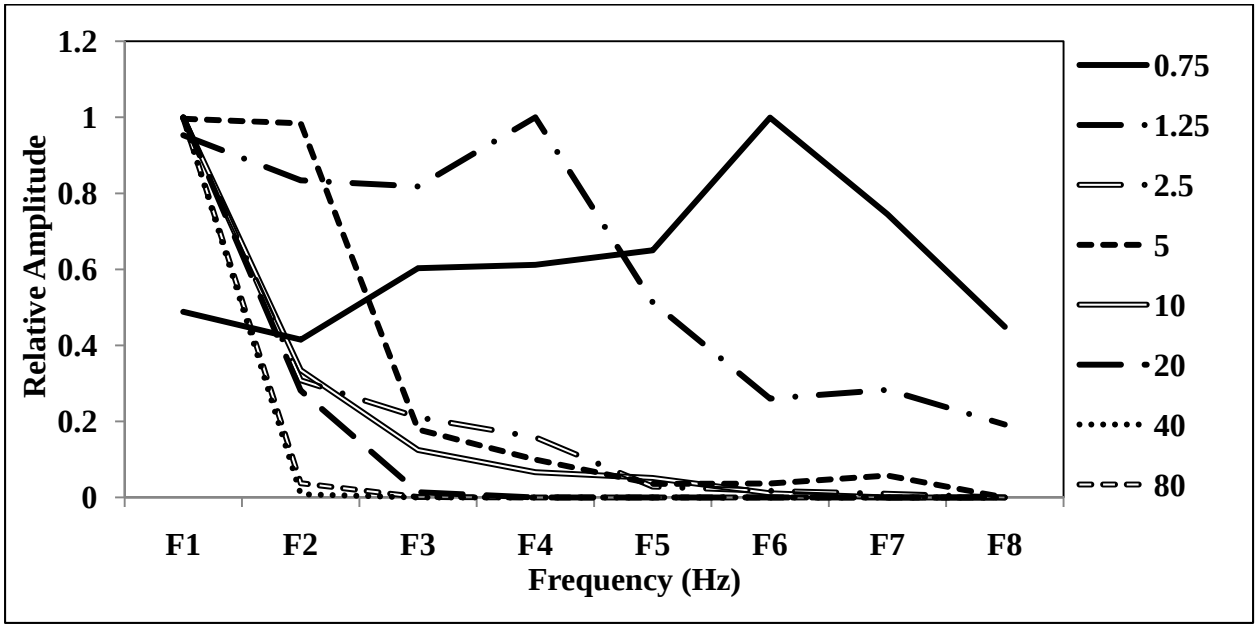


Figure 30 Harmonic structure adults awake

An analysis of the harmonic sum of the response (cf. Subsection 4.3.3) reveals that the overall amplitude of the response decreased as modulation frequency increased from 0.75 to 80 Hz (Figure 31).

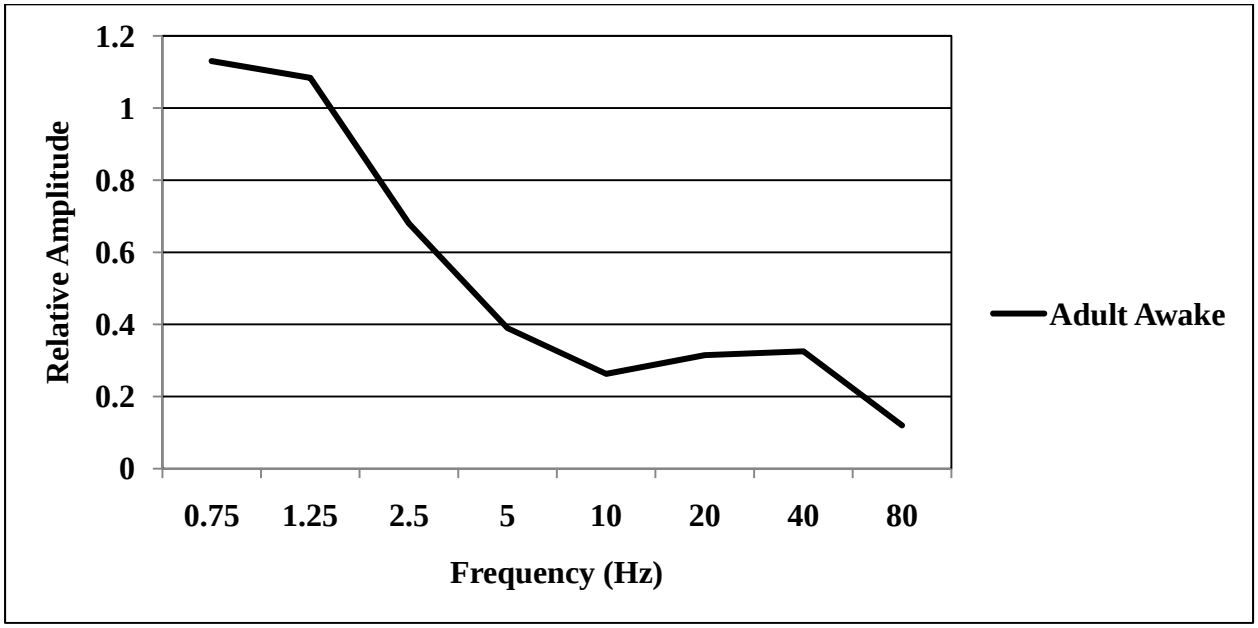


Figure 31 Harmonic sum adults awake

5.2.1.2 Children

Grand averages of the ASSR power spectra at various modulation frequencies are displayed separately in Figures 32 through 39. The total response and the estimated background noise have been superimposed in each of the representative figures for children, and for children and adults for direct comparison.

When F1=0.75 Hz, the averaged steady-state response was represented by a series of spectral components at integer multiples of the fundamental frequency that corresponded to those that were revealed in the adult response. The averaged response obtained in children was substantially larger compared to adults. There were 12 spectral components that were identified and were considered to be equal to or greater than the estimated background noise in children, compared to 16 components observed in the adult response. However, in children the averaged response demonstrated a redistribution of power in the spectrum, such that, the power of the response shifted toward the lower harmonics. Thus, of the 12 spectral components identified, the highest amplitude was shifted from the sixth harmonic (4.5 Hz) for adults to the third harmonic (2.25 Hz) in children. The lowest amplitude (i.e. highest frequency component detectable) shifted from the 16^{th} harmonic (12 Hz) for adults to the 15^{th} harmonic (11.25 Hz) in children.

Similarly, when F1=1.25 Hz, the averaged steady-state response was represented by several components that were harmonically related in and around the fundamental frequency that corresponded to those revealed in the adult response. The averaged response was substantially larger in children. There were 11 spectral components identified in children, compared to 12 components observed in the adult response. Similar to the redistribution of power in the spectrum at 0.75 Hz, the averaged response at 1.25 Hz shifted toward the lower harmonics. Thus, of the 11 spectral components identified, the highest power shifted from fourth harmonic (5.0 Hz) for adults to the second harmonic (2.5 Hz) in children. In addition, the lowest power shifted from the 12^{th} harmonic (15 Hz) for adults to 11^{th} harmonic (13.75 Hz) in children.

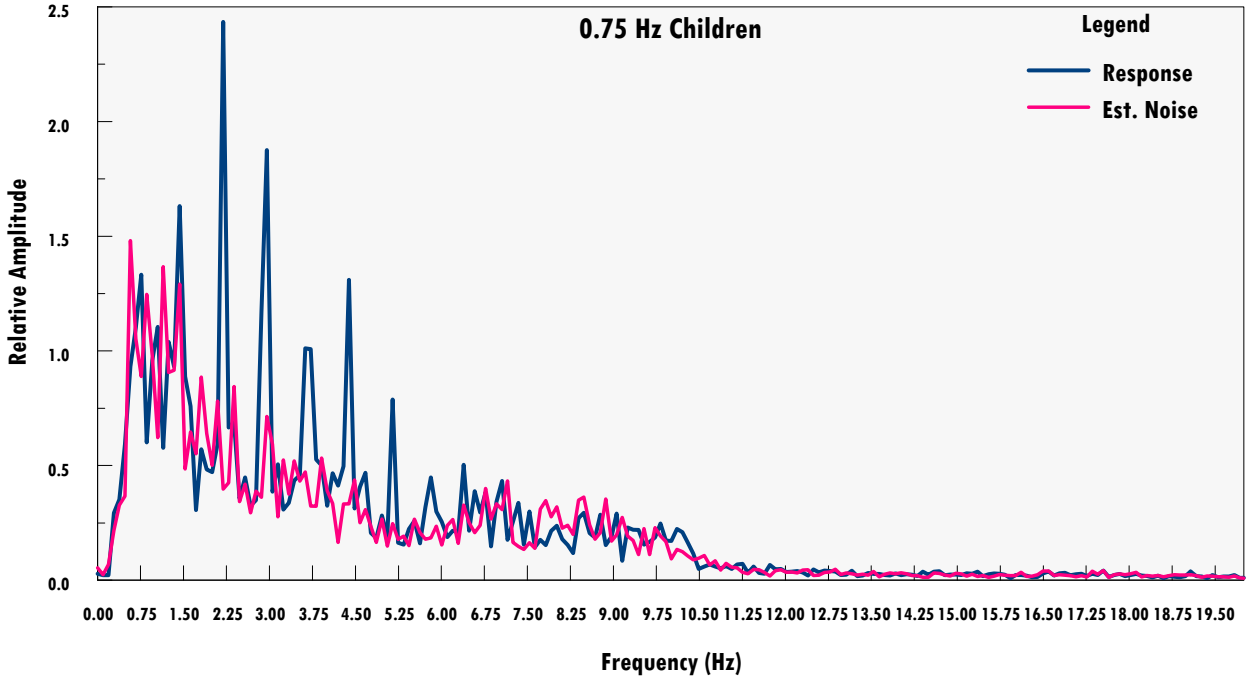
Likewise, when F1=2.5 Hz, the averaged steady-state response was represented by a series of spectral components at integer multiples of the fundamental frequency that corresponded to those revealed in the adult response. The averaged response was considerably

larger in children compared to adults. Like the response observed in adults, there were six spectral components that were identified in children. Of these six spectral components identified, the highest power remained at the fundamental frequency (2.5 Hz), and lowest power remained at the seventh harmonic (17.5 Hz).

When F1=5 Hz, the averaged responses were represented by several components that were harmonically related in and around the fundamental frequency that were identical to those revealed in the adult response. The averaged response at 5 Hz was considerably larger in children compared to adults. Although the spectral content of the response in children revealed trends that were identical to those observed at 5 Hz in adult responses, the averaged response in children demonstrated a redistribution of power in the spectrum. This new distribution of power repositioned the integer that demonstrated the highest amplitude from the fundamental and second (5 and 10 Hz) harmonic in adults, to exclusively the fundamental frequency in children. Conversely, when F1=10 Hz, the averaged steady-state response was represented by a series of spectral components at integer multiples of the fundamental frequency that corresponded to those revealed in the adult response. The averaged steady-state response at 10 Hz was noticeably larger in children compared to adults. There were three clear spectral components that were identified in children, compared to six components observed in the adult response. Of the three spectral components identified, the highest power remained at the fundamental frequency; however, the integer that demonstrated the lowest power shifted from the sixth harmonic (60 Hz) for adults to the third harmonic (30 Hz) in children.

Likewise, when F1=20 Hz, the averaged response was represented by several components that were harmonically related in and around the fundamental frequency that corresponded to those revealed in the adult response. Unlike the other modulation frequencies,

the averaged response at 20 Hz was considerably smaller in children compared to adults. There were two spectral components were identified in children, compared to three components observed in the adult response. Of the two spectral components identified, the highest power remained at the fundamental frequency (20 Hz); however, the integer that demonstrated the lowest power shifted from the third harmonic (60 Hz) for adults to the second harmonic (40 Hz) in children. Conversely, when F1=40 Hz and 80 Hz the spectral content of the response in children revealed trends that were identical to those observed at corresponding modulation frequencies for adults. Even so, the averaged response obtained at 40 Hz was considerably smaller when measured at the fundamental frequency in children compared to adults



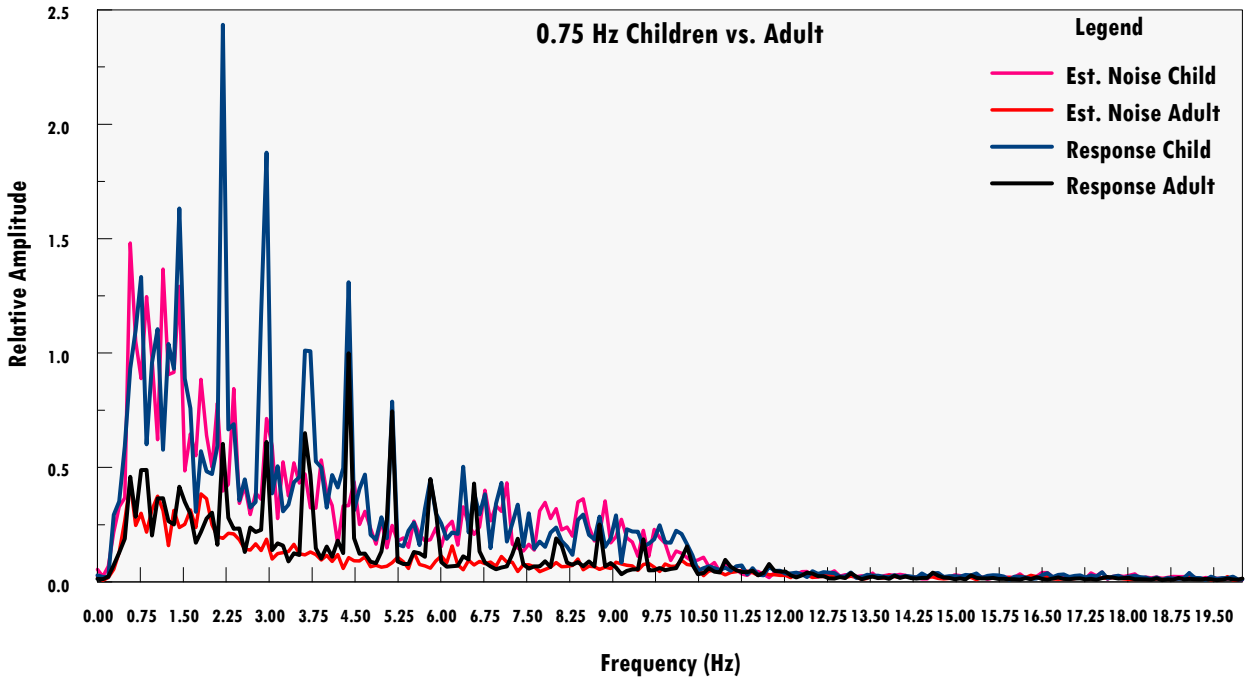
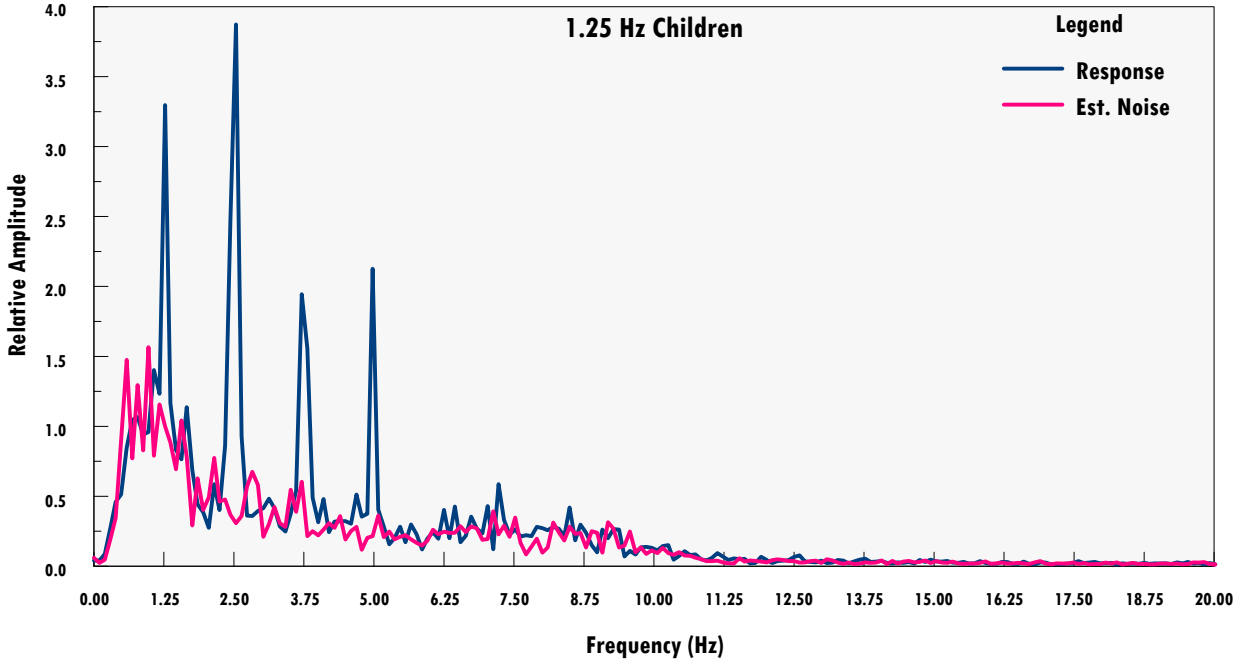


Figure 32 Grand averages at 0.75 Hz children and comparison



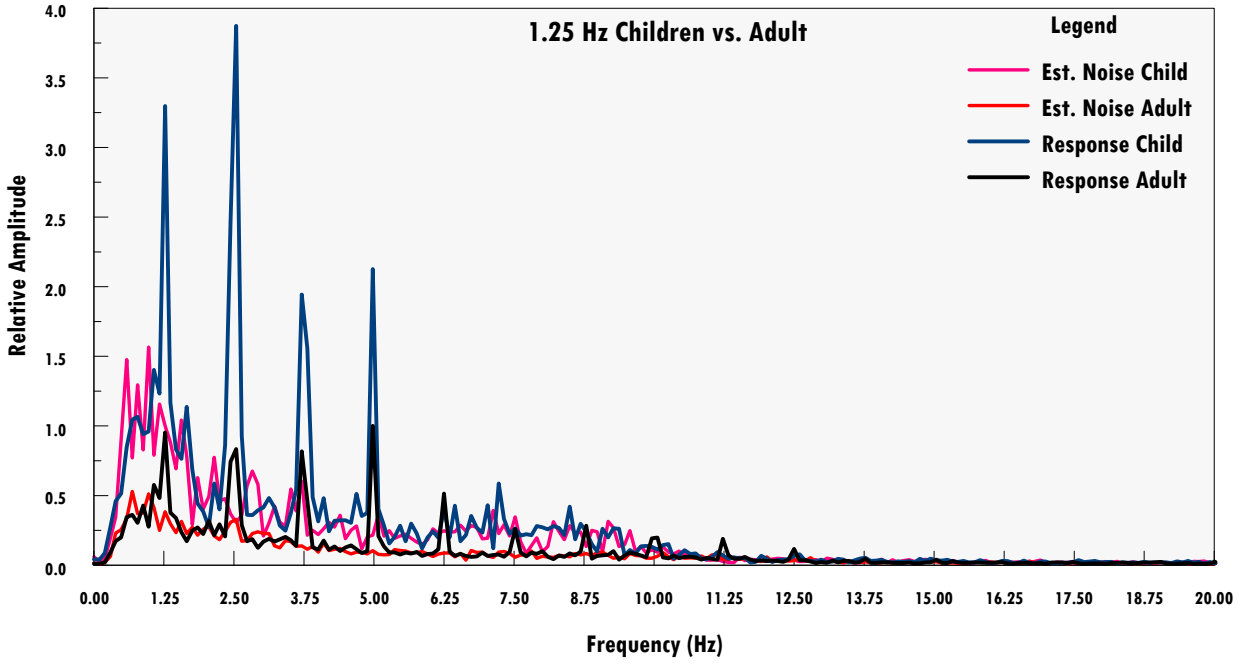
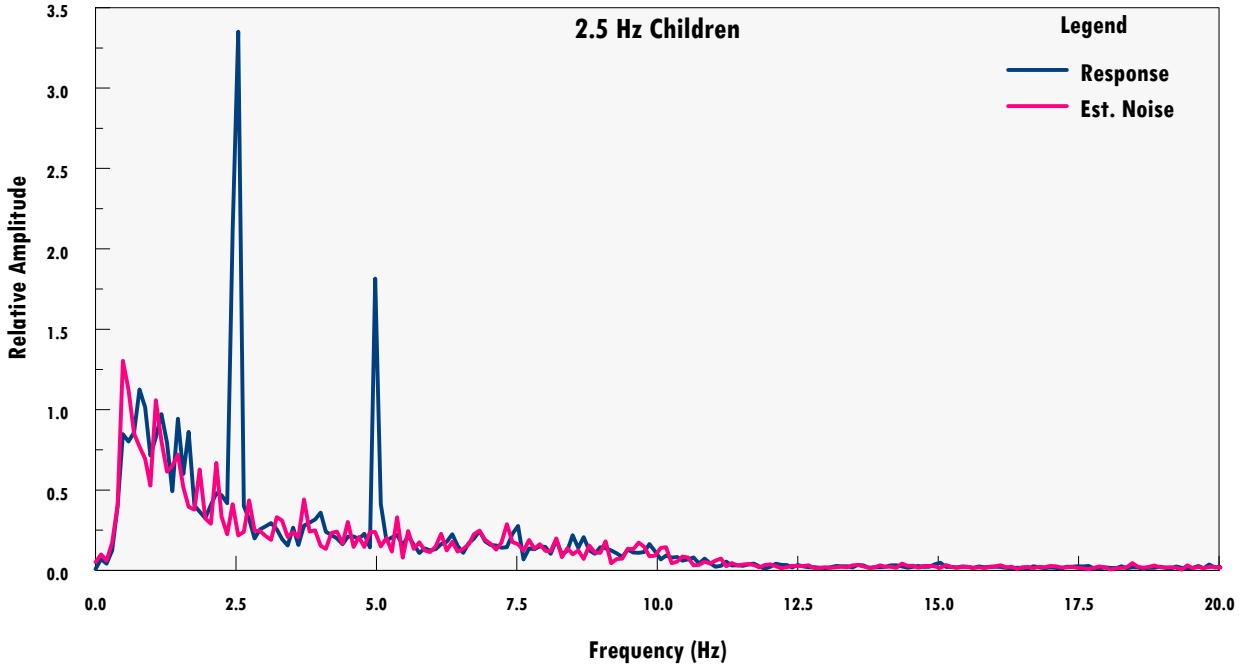


Figure 33 Grand averages at 1.25 Hz children and comparison



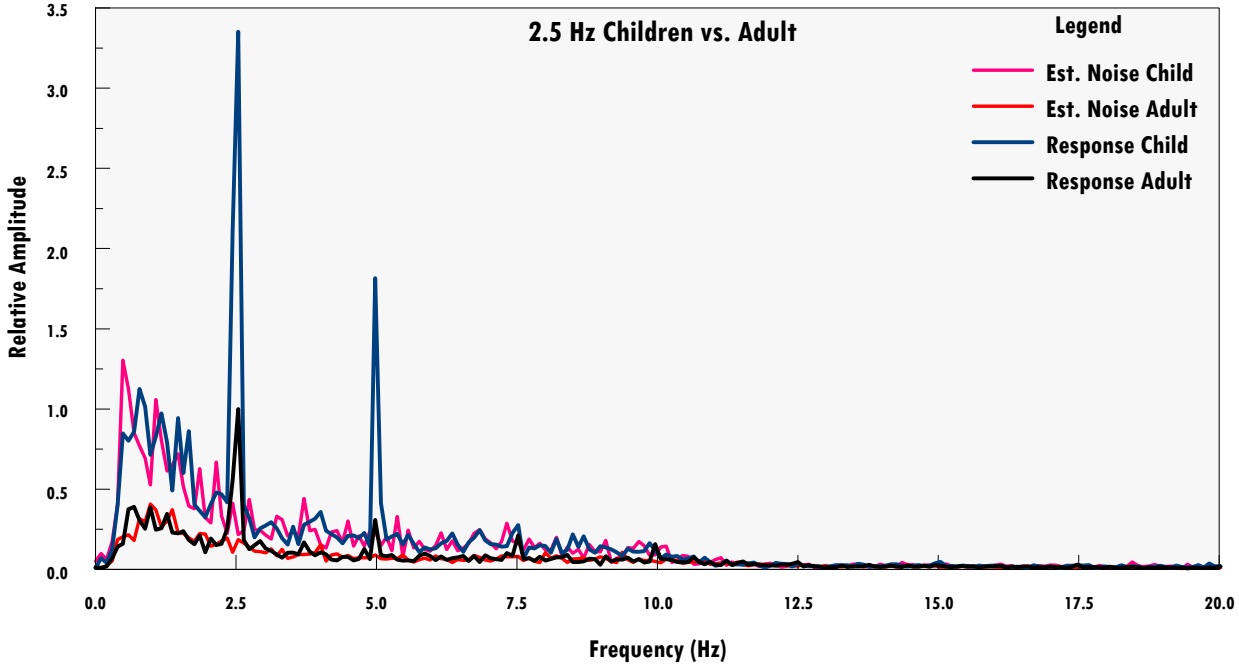
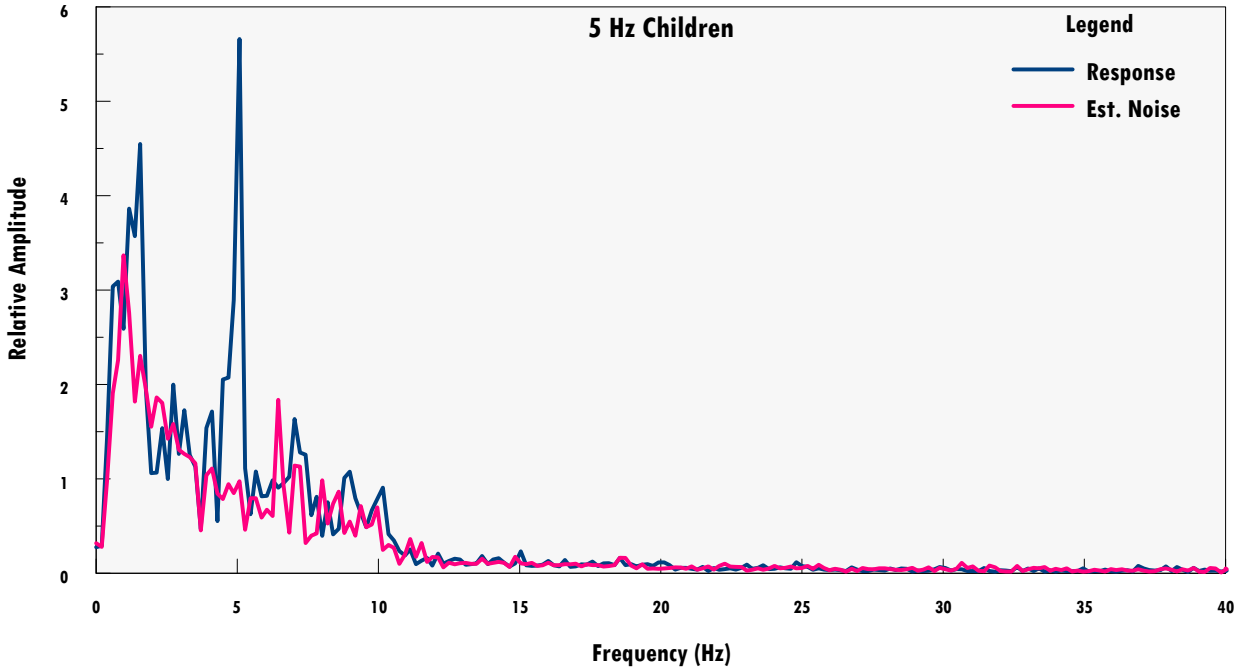


Figure 34 Grand averages at 2.5 Hz children and comparison



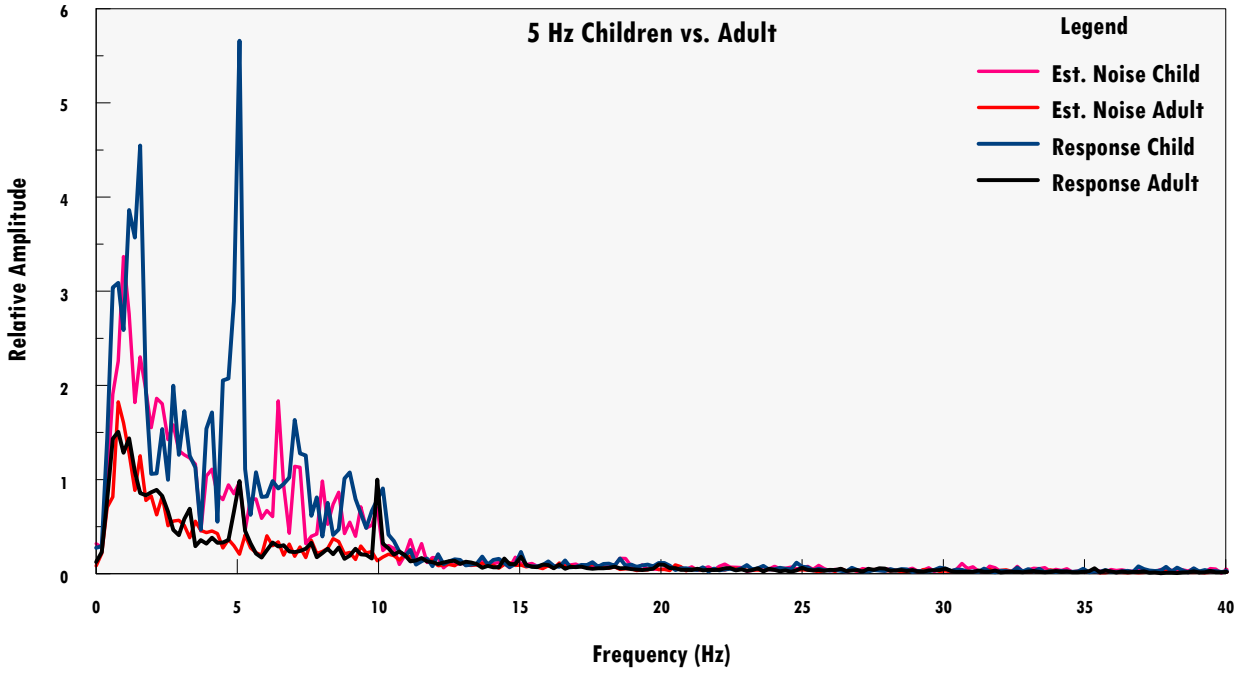
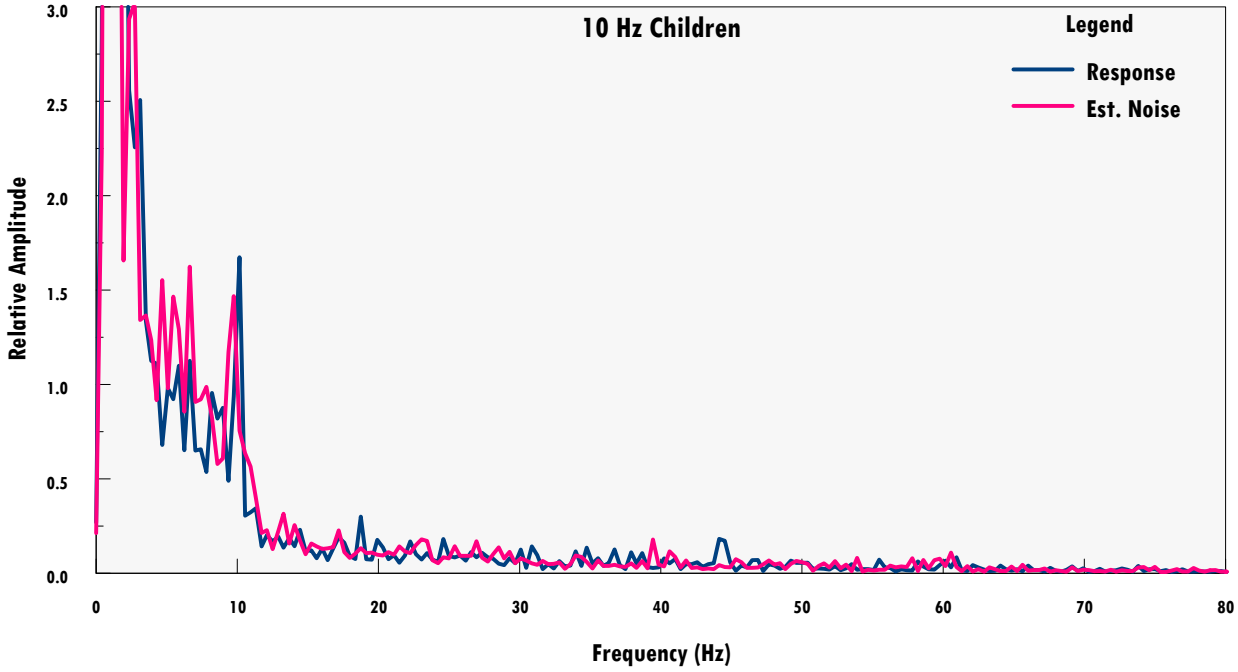


Figure 35 Grand averages at 5 Hz children and comparison



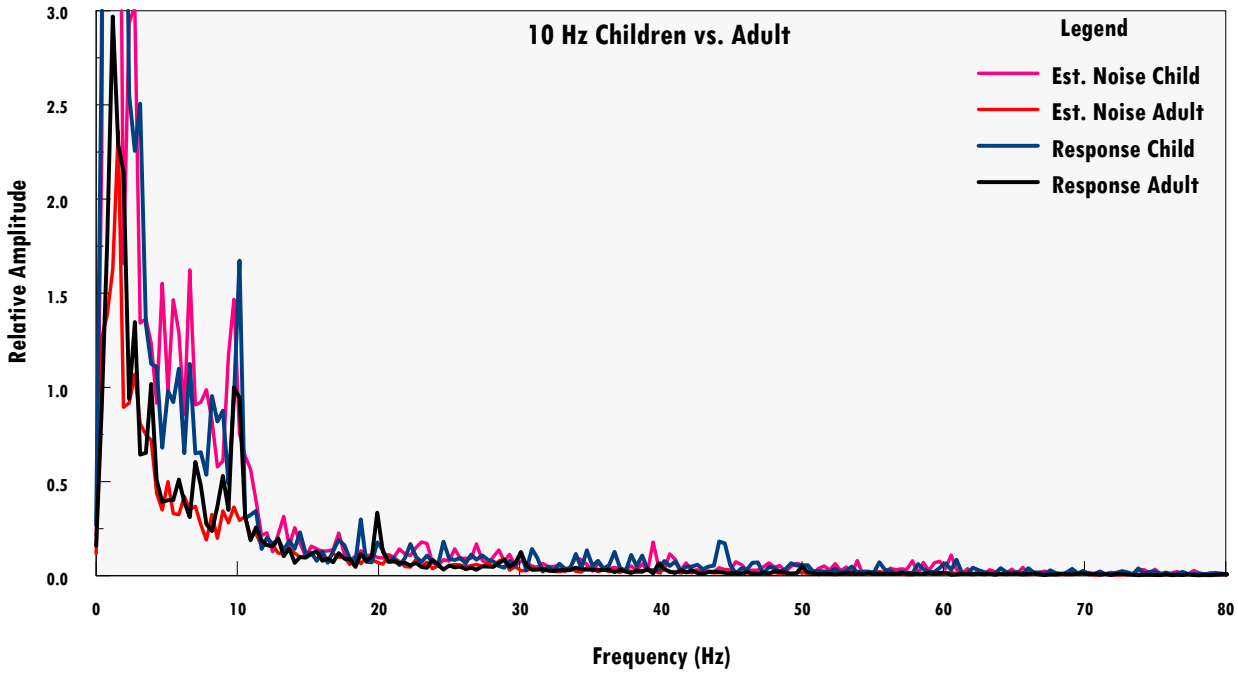
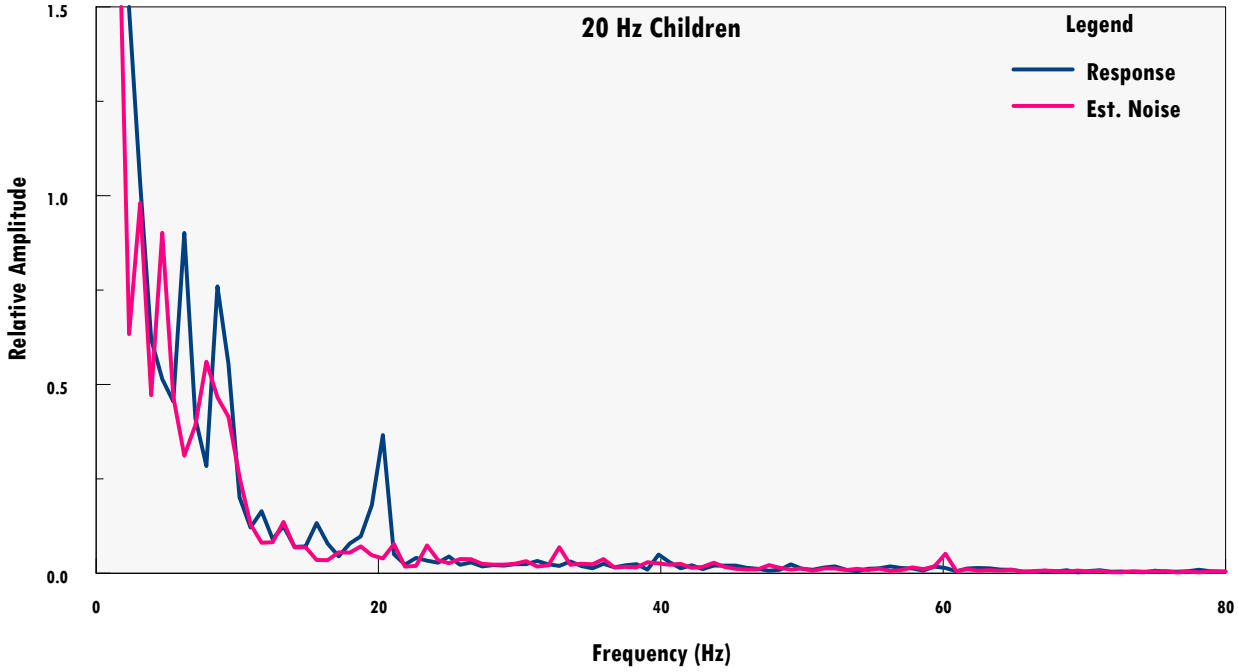


Figure 36 Grand averages at 10 Hz children and comparison



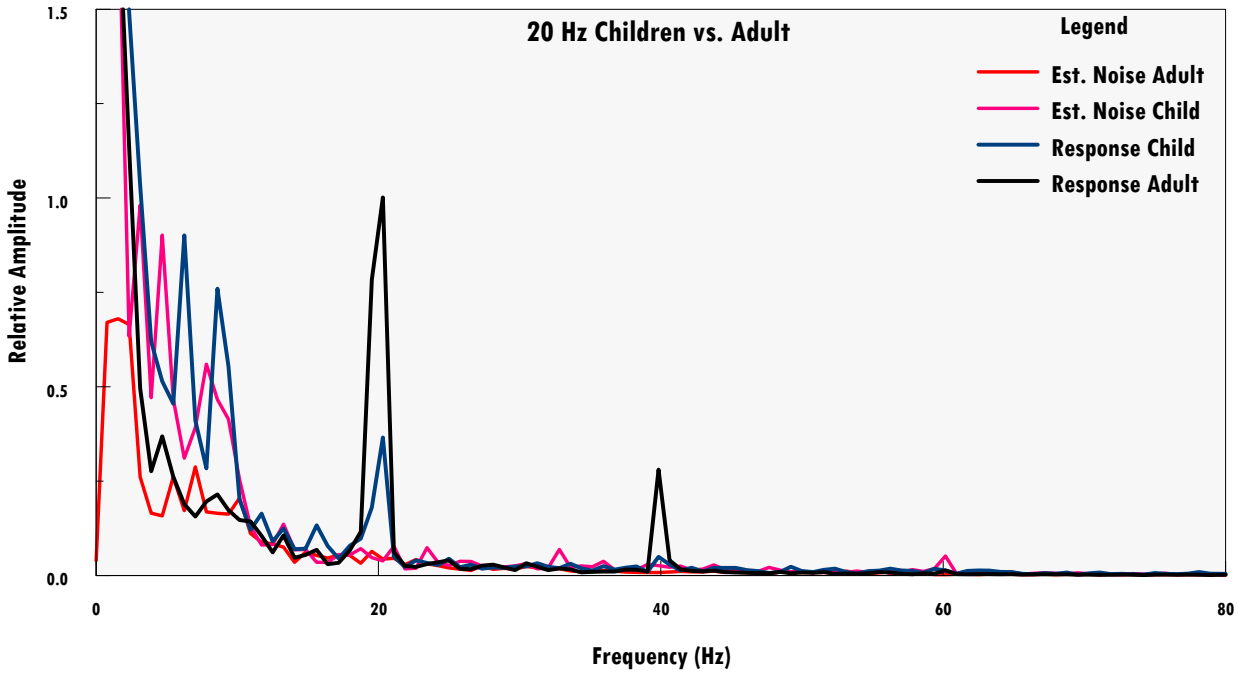
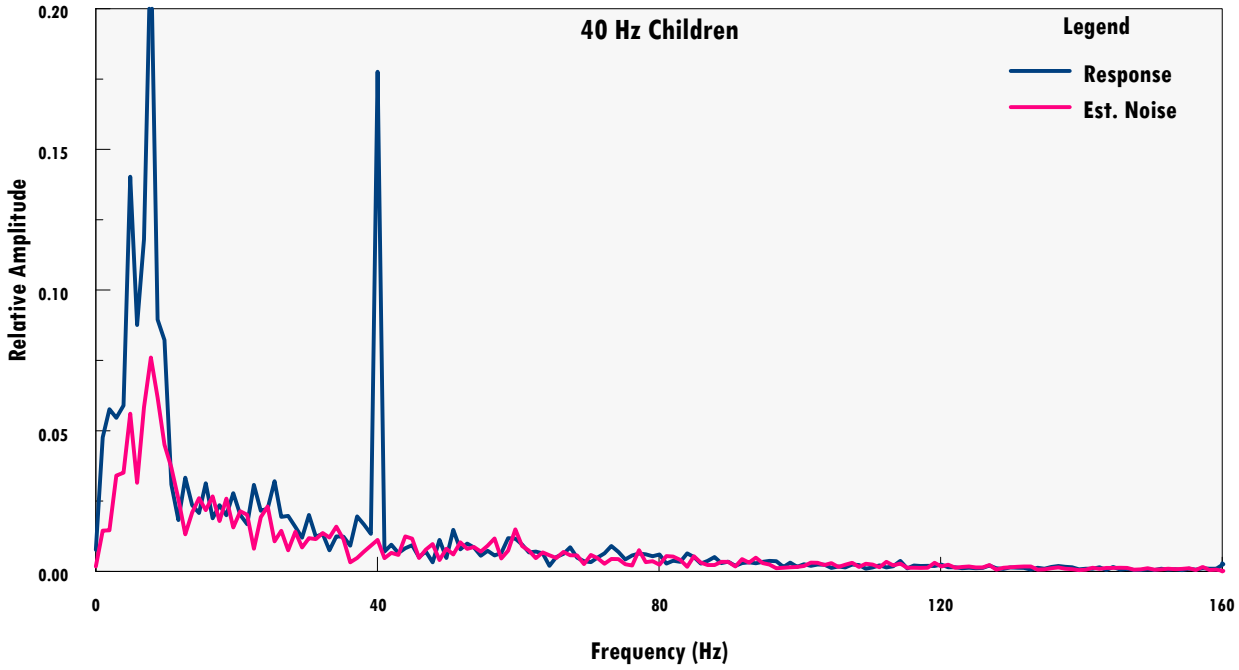


Figure 37 Grand averages at 20 Hz children and comparison



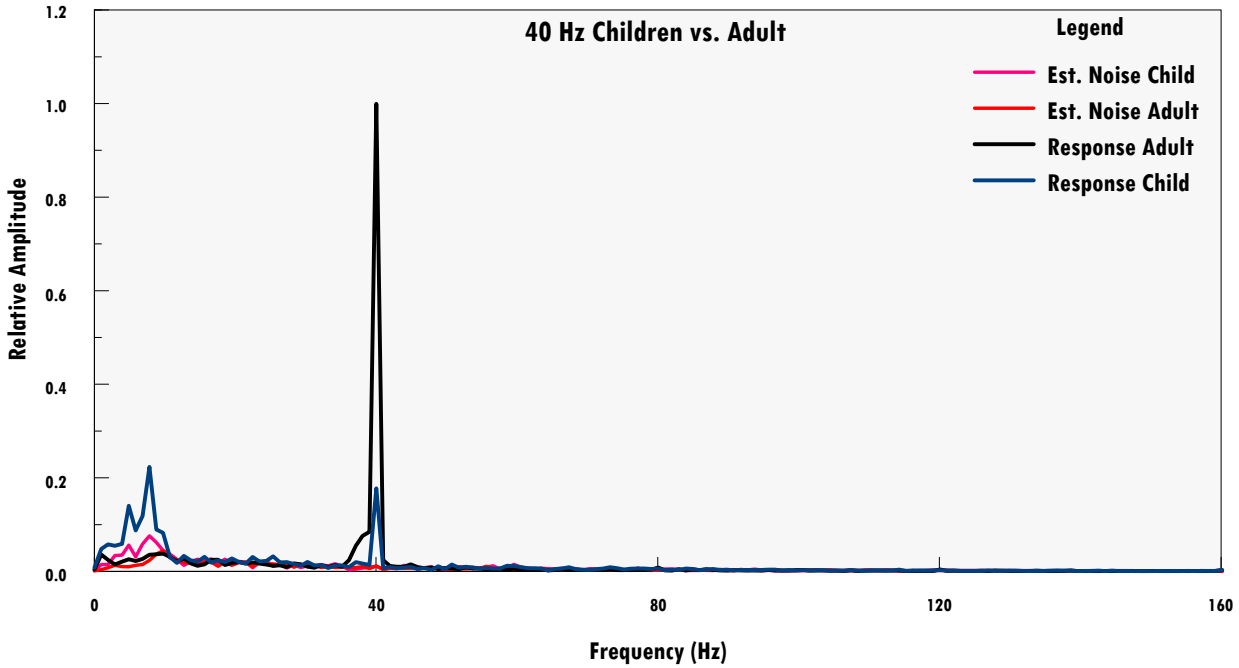
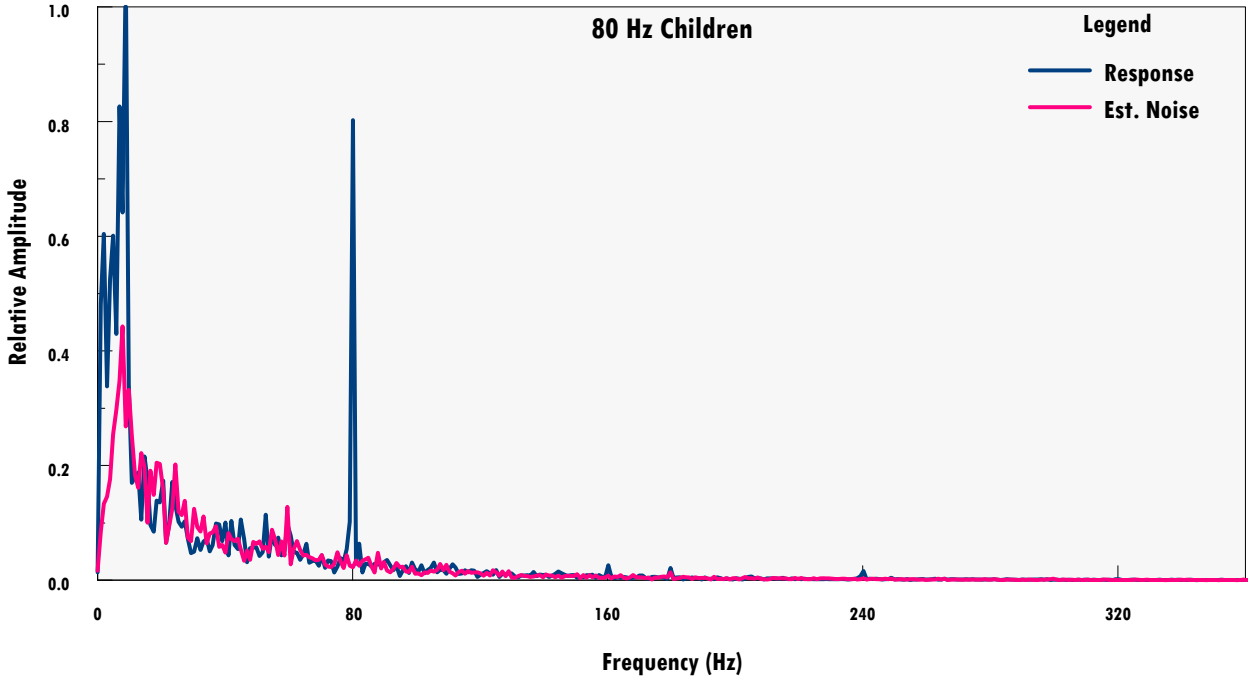


Figure 38 Grand averages at 40 Hz children and comparison



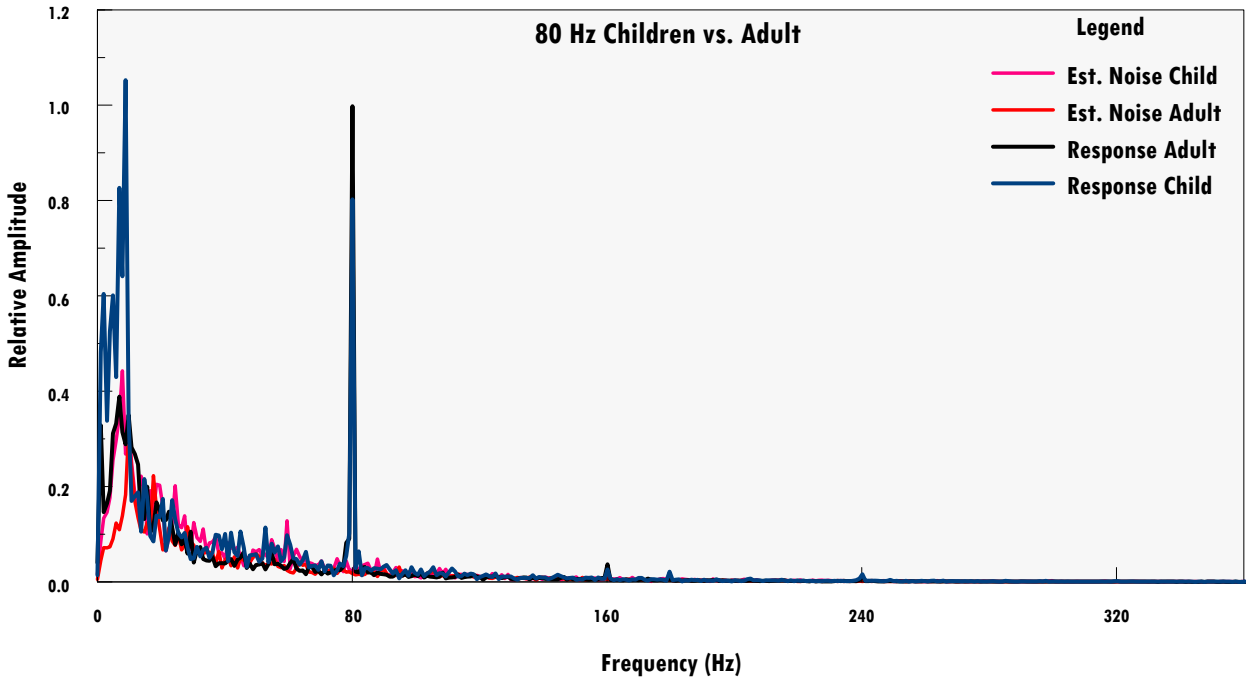
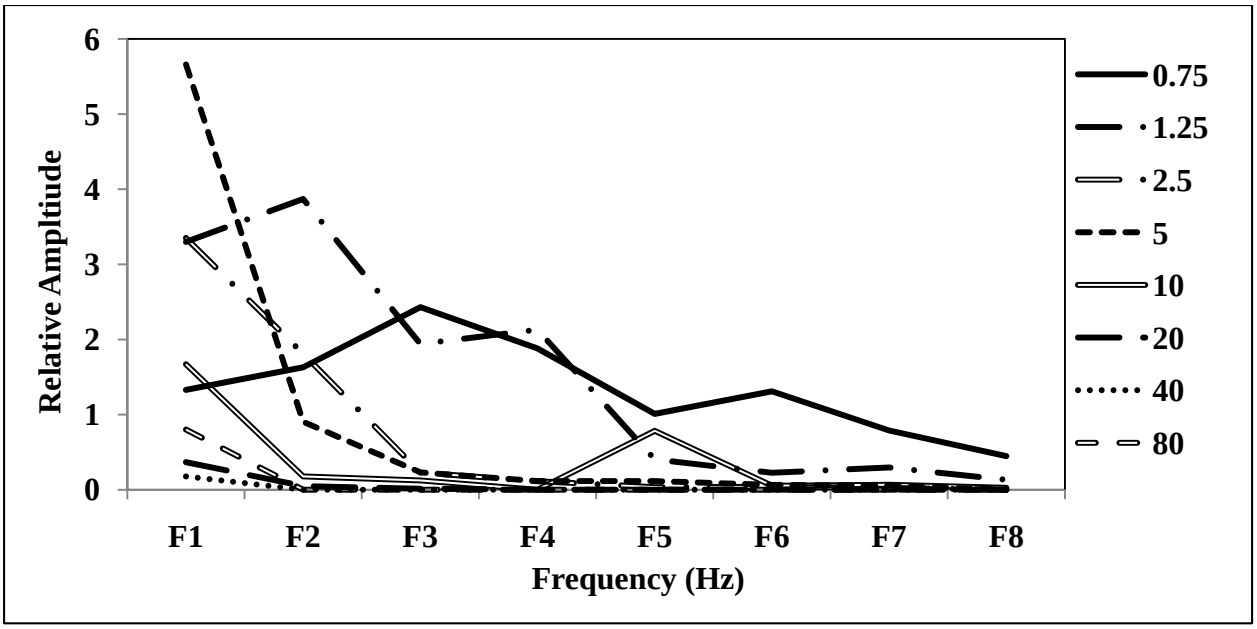


Figure 39 Grand averages at 80 Hz children and comparison

Examination of the first eight harmonics from each spectrum well reflects the harmonic structure of the averaged responses across modulation frequency (Figure 40). The overall structure of the averaged responses in children revealed trends that were similar to those observed when adults were tested while awake. That is, that the number of harmonically related frequency components that were identified decreased as modulation frequency increased from 0.75 to 80 Hz. In addition, the power of the spectra was highest at the third harmonic at 0.75 and the second harmonic at 1.25 Hz, whereas, the power of the spectra was highest at the fundamental frequency at modulation frequencies from 2.5 and above. A closer inspection of the averaged responses in adults (black) compared to children (blue) at modulation frequencies of less than 10 Hz, revealed substantial differences in the relative amplitudes of the responses, especially at 0.75, 1.25 and 5 Hz.



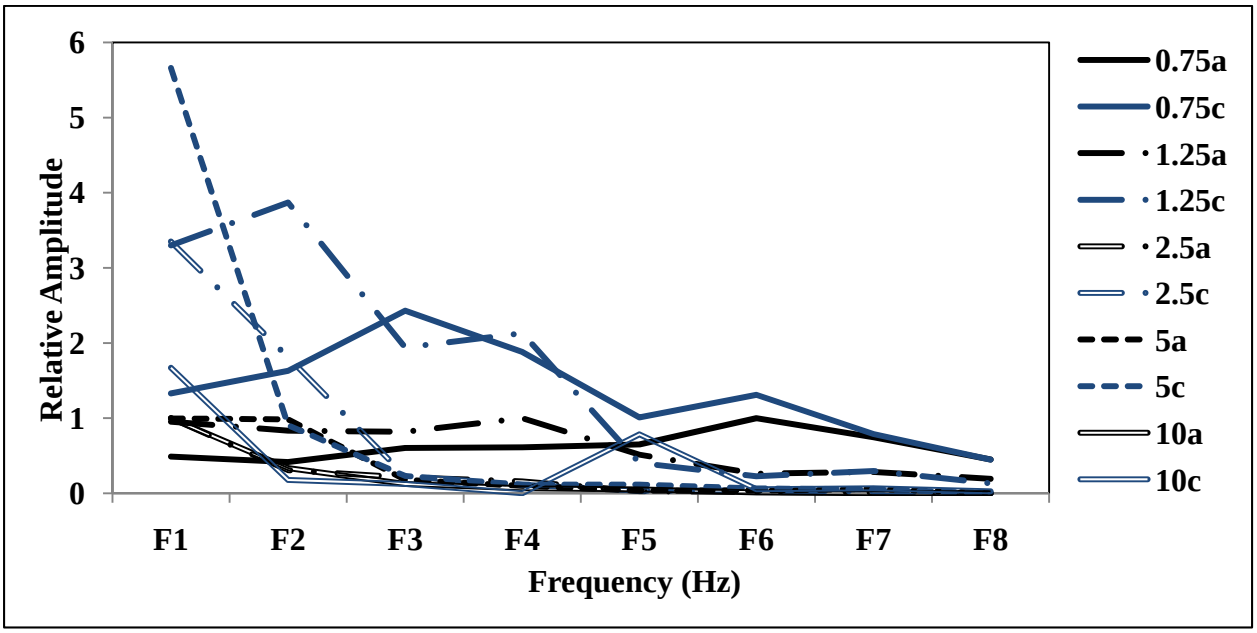


Figure 40 Harmonic structure children

In addition, an analysis of the harmonic sum of the response (Figure 41) reveals trends that were similar to those observed in adults. Namely, the overall amplitude of the response decreased as modulation frequency increased from 0.75 to 80 Hz. In addition, when the harmonic sum for children (blue) and adults (black) were superimposed, differences in the relative amplitudes of the responses were seen at the modulation frequency extremes. Substantial differences were seen at 0.75, 1.25, 2.5 and 5 Hz, in which the harmonic sum of the response was larger for children compared to adults. Likewise, considerable differences were seen at 20 and 40 Hz, in which the harmonic sum was smaller in children compared to adults. No appreciable differences between the two groups were observed at 10 and 80 Hz.

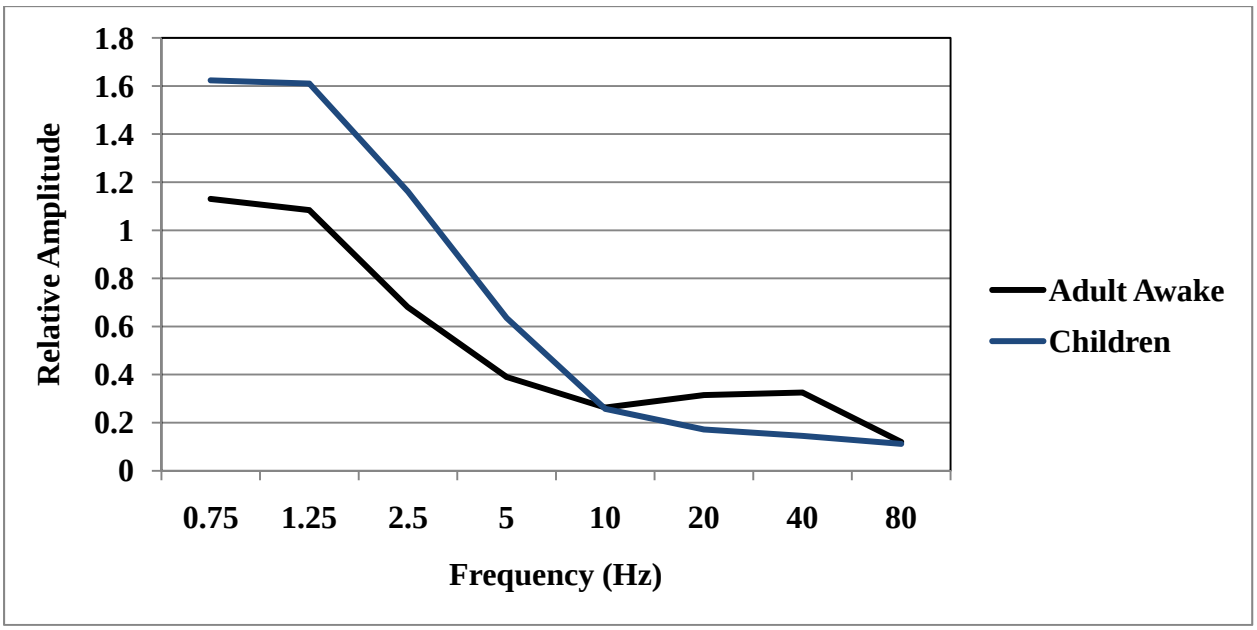


Figure 41 Harmonic sum children

Because there was difference in sample size between adults (n = 25) and children (n = 12), a follow-up analysis addressed the possibility that the differences found in the harmonic sum of the response was due to sample size. Thus, to estimate test-retest reliability on the harmonic sum of the response between the two groups, the adult data were divided into equivalent halves (i.e., we randomly chose the data from 12 adults when tested while awake [sample 1] and then randomly chose another 12 from the remaining 13 [sample 2]), then computed and compared the means and standard errors among the data sets, children versus adult sample 1, and children versus adult sample 2. Visual inspection of Figure 42 reveals good agreement between adult results, indicating that substantial differences still occur in the child data over either adult sub-sample despite the reduced number of the adult subjects.

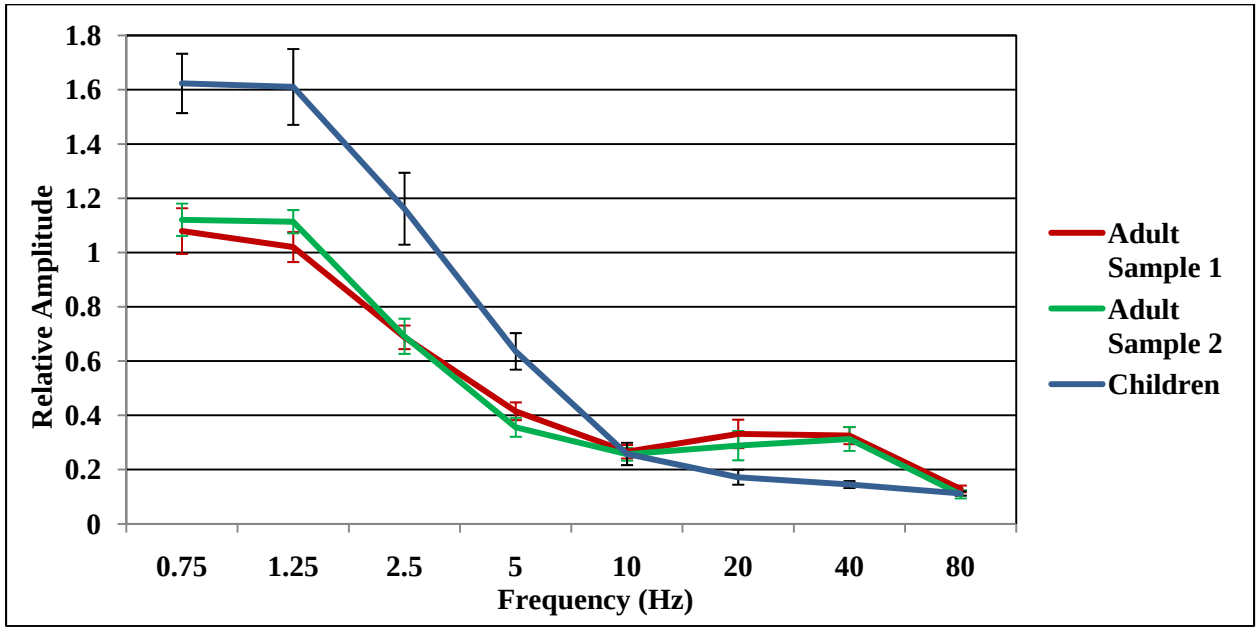


Figure 42 Test-retest reliability regarding harmonic sum

Specific Aim 1: Examine the effects of repetition (modulation) rate (frequency) on ASSR amplitude in adults and in children to (b) define the repetition rate(s) which evoke(s) the maximal response amplitude as a function of age.

A two-way analysis of variance (ANOVA) (age group by repetition rate) was conducted to evaluate the effects of age group, repetition rate, and the interaction between these two variables on response amplitude. Mauchly's test indicated that the assumption of sphericity had been violated (χ^2 (27) = 151.44, $p < 0.001$), therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity (ε = .519). A significant main effect was observed for repetition rate by age group F (1, 35) = 20.5, $p < .001$, partial $\eta^2 = .369$. Likewise, a significant main effect was observed for repetition rate F (3.6, 127.20) = 226, $p < 0.001$, partial $\eta^2 = 0.866$. Thus, the average response of adults (across repetition rates) is different than the average response of children (across repetition rates). In addition, the interaction between age group and repetition rate was also significant F (3.6, 127.20) = 18.58, $p < 0.001$, partial $\eta^2 = 0.347$.

The significant interaction was followed by tests of simple main effects. Independent samples t-tests were conducted to compare the responses of adults and children at each repetition rate. An alpha of .01 was used for these comparisons. Table 27 shows the means and SDs for adults and children across repetition rates. Results revealed that the mean response for children was significantly higher than the mean response for adults at 0.75 Hz (t = -4.402, p = .000), at 1.25 Hz (t = -3.636, p = .003), at 2.5 Hz (t = -3.492, p = .004), and at 5 Hz (t = -4.290, p = .000).

Table 27 Means and SD for Adults and Children across Modulation Frequencies

Rate	Group	Mean	SD
0.75	Adult	1.13E-06	2.87E-07
	Child	1.62E-06	3.79E-07
1.25	Adult	1.08E-06	1.90E-07
	Child	1.61E-06	4.84E-07
2.5	Adult	6.80E-07	1.89E-07
	Child	1.16E-06	4.59E-07
5	Adult	3.90E-07	1.18E-07
	Child	6.36E-07	2.34E-07
10	Adult	2.63-07	8.07E-08
	Child	2.58E-07	1.42E-07
20	Adult	3.15E-07	1.80E-07
	Child	1.72E-07	9.52E-08
40	Adult	3.25E-07	1.31E-07
	Child	1.45E-07	4.47E-08
80	Adult	1.20E-07	4.73E-08
	Child	1.12E-07	2.79E-08

5.3 WITHIN- AND BETWEEN- TEST SESSION RELIABILITY

Specific Aim 1: Examine the effects of repetition (modulation) rate (frequency) on ASSR amplitude in adults and in children to (c) demonstrate overall consistency and stability of response measurements across time points.

5.3.1 Temporal Analysis of quasi-steady-state responses

5.3.1.1 Adults awake

The within-test session reliability at 0.75 Hz is displayed in Figure 43. Visual inspection reveals that the relative amplitude of the retest (green) was nearly identical to the grand averaged results obtained in the original test (black). Also displayed is the between-test session accuracy at 40

Hz. Similarly, no appreciable effect on the relative amplitude of the response was observed in the retest compared to the original grand averaged results obtained at 40 Hz.

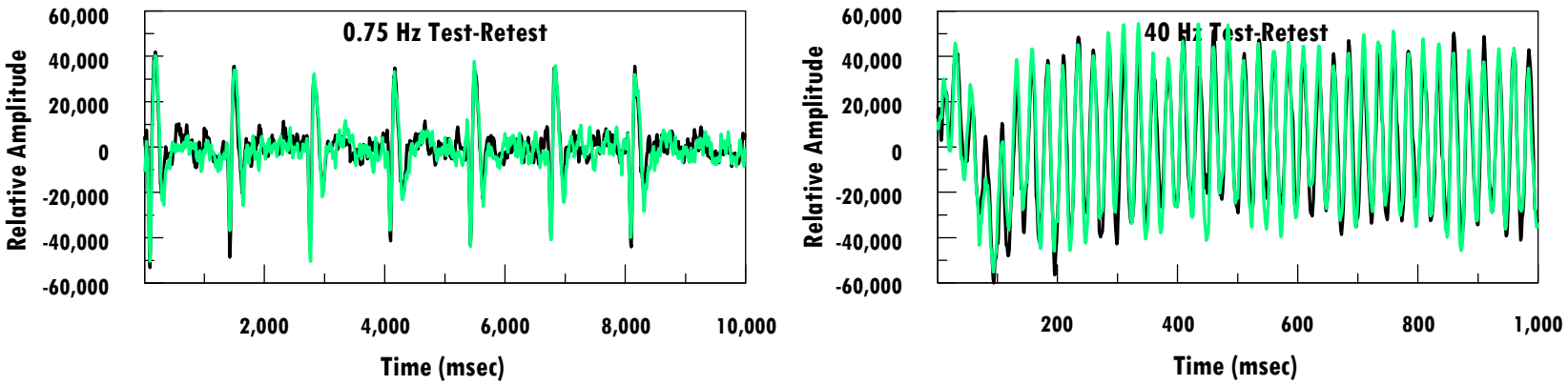


Figure 43 Temporal within- and between-test session reliability in adults

5.3.1.2 Children

The test-within session reliability at 0.75 Hz is displayed in Figure 44. Visual inspection reveals that the relative amplitude of the response in the retest (green) was somewhat smaller, but nearly identical to the grand averaged response obtained in the original test (black).

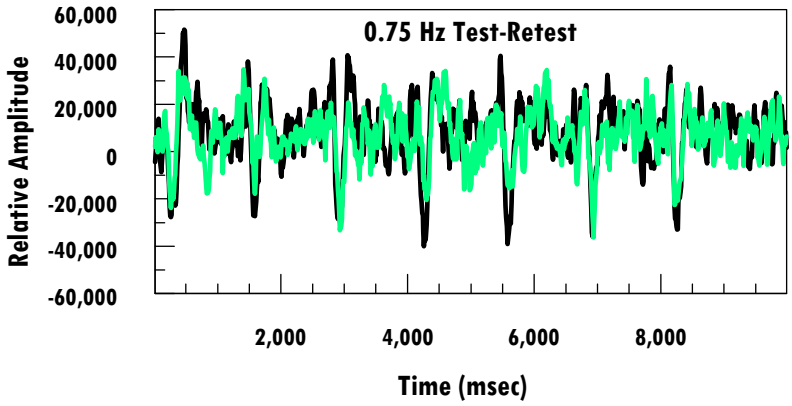


Figure 44 Temporal within-test session reliability in children

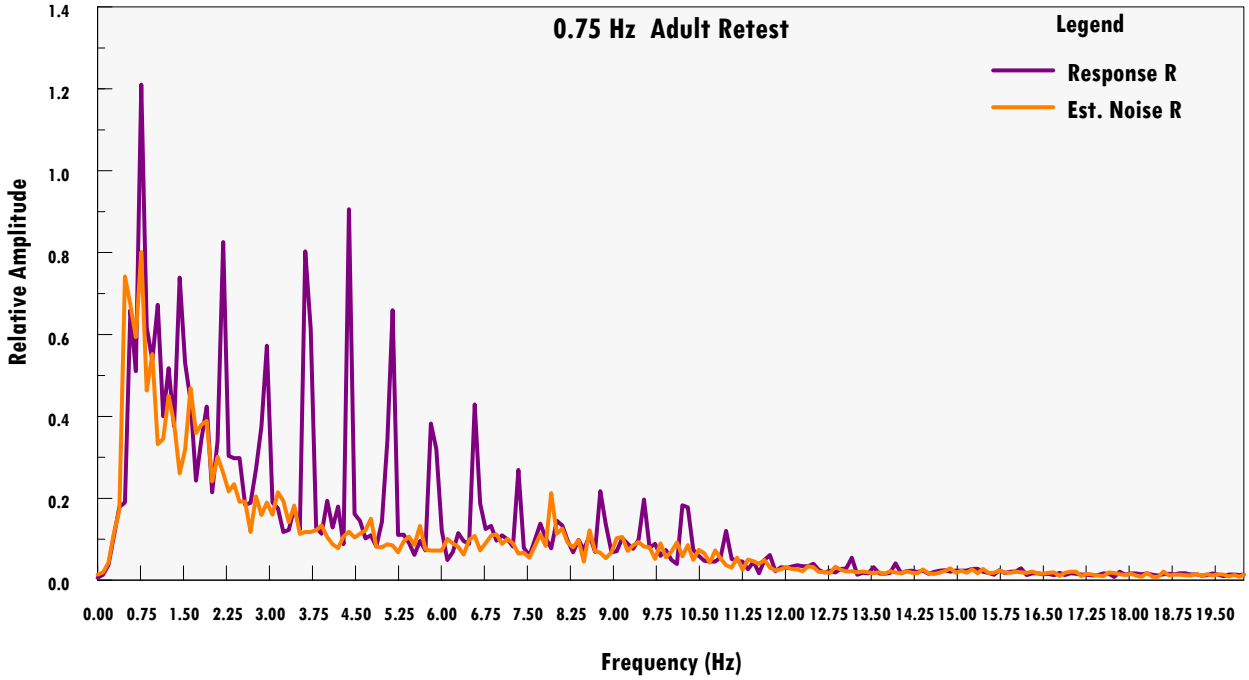
5.3.2 Spectral Analysis of quasi-steady-state responses

5.3.2.1 Adults

The within-test session accuracy at 0.75 Hz (Figure 45) revealed a series of spectral components at integer multiples of the fundamental frequency that were identical to those revealed in the original test. Likewise, the relative amplitude of the retest was nearly identical to the averaged results obtained in original test. However, unlike the original test at 0.75 Hz, the averaged

responses of the retest demonstrated a redistribution of power in the spectrum, such that, the power of the response was shifted toward the lower harmonics. This new distribution of power repositioned the integer that demonstrated the highest amplitude from the sixth harmonic (4.5 Hz) for the original test to the fundamental frequency in the retest; however, the integer that demonstrated the lowest amplitude remained at the 15^{th} harmonic (11.25 Hz). Moreover, the estimated background noise appeared to have increased proportionally to the shift in power toward the lower harmonics. Otherwise, the increase in the estimated background noise was negligible in the retest compared to the original test. Similarly, the between-test session accuracy at 40 Hz revealed that the spectral content in the retest was identical to the original test (Figure 46). The spectral power of the averaged response was still dominated by the fundamental frequency. However, the relative amplitude of the fundamental frequency was slightly larger in the retest compared to the original test.

Pearson's product-moment correlation coefficients were computed to assess overall consistency and stability of within- and between-test session response measurements for adults. A moderate positive correlation was found (r (25) = .504, $p < .001$), indicating a significant linear relationship in the within-test session responses at 0.75 Hz. In addition, a strong positive correlation was found (r (25) = .927, p = .012), indicating a significant linear relationship in the between-test session accuracy at 40 Hz. Intraclass correlation coefficient (ICC) was also analyzed to quantify the proportion of the variance in responses that can be attributed to "true" variation among individuals. It was found that ICC (2, 1) = .451, p = .009 at 0.75 Hz, and ICC (2, 1) = .927, $p < .001$ at 40 Hz. Therefore, for adults the ICC revealed excellent agreement at 40 Hz but, only fair agreement at 0.75 Hz.



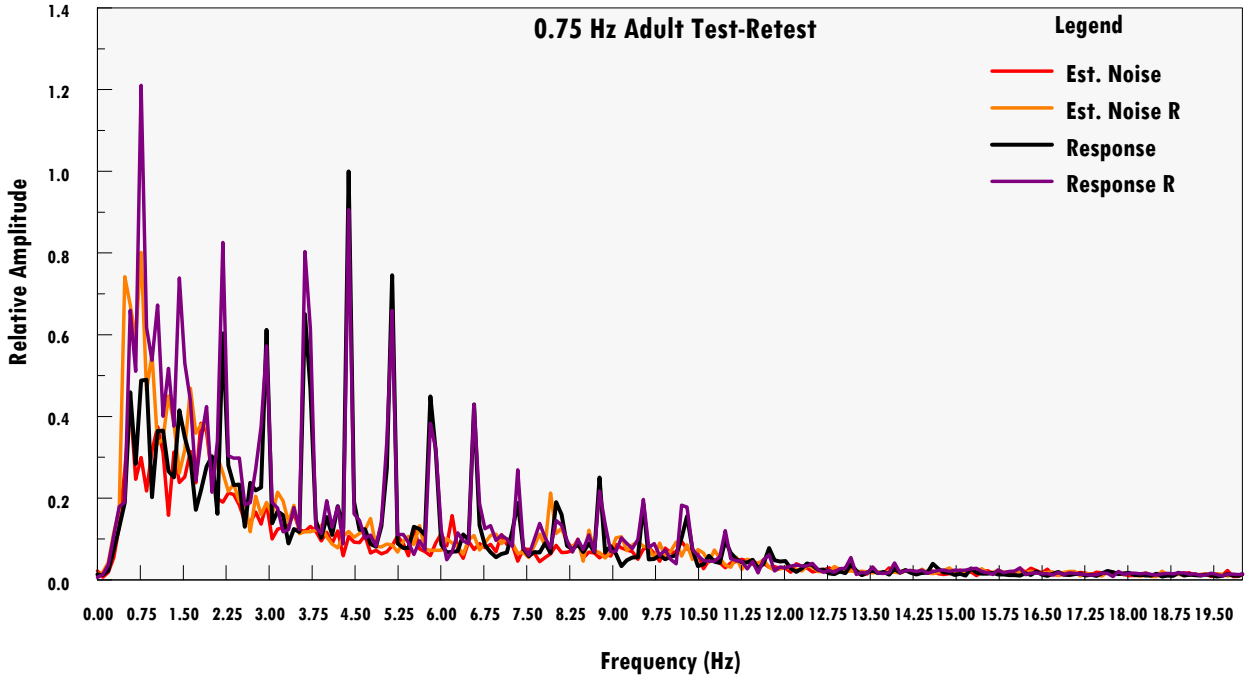
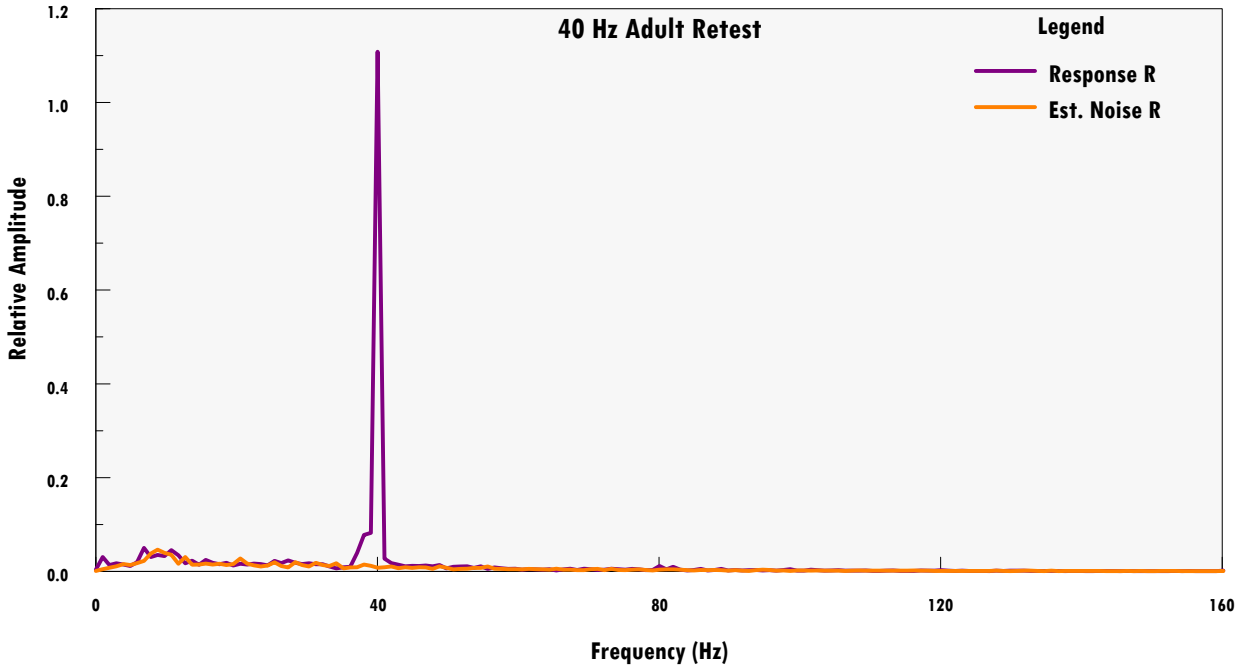


Figure 45 Spectral within-test session reliability adults awake



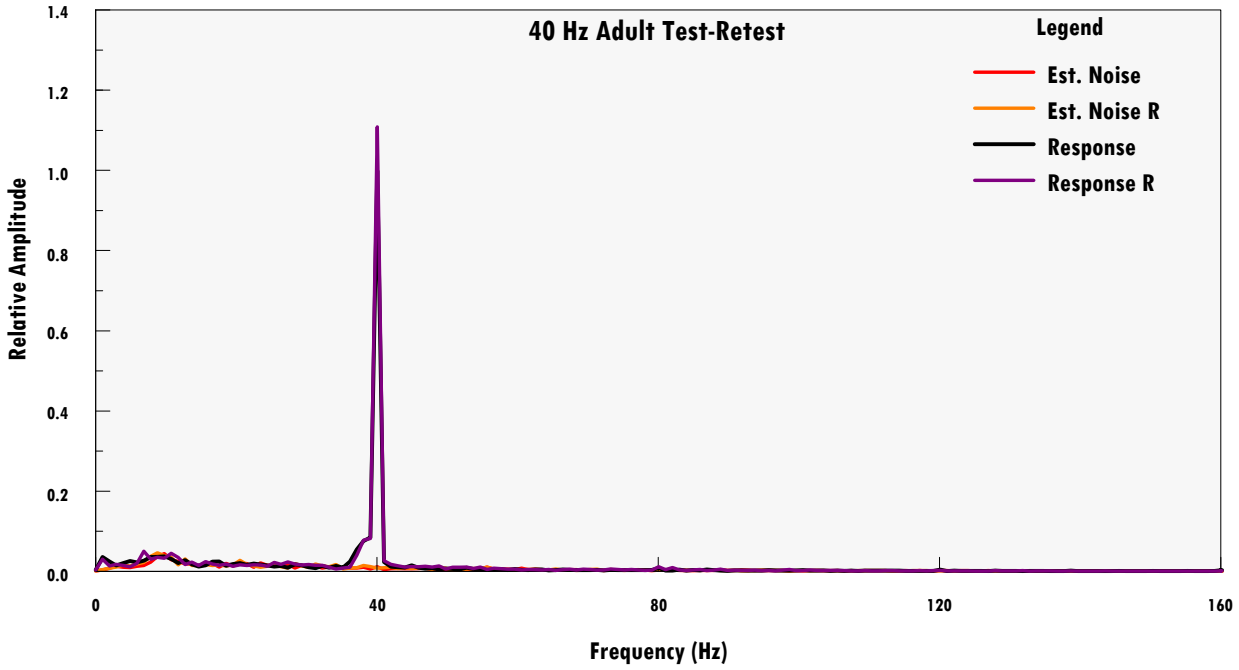
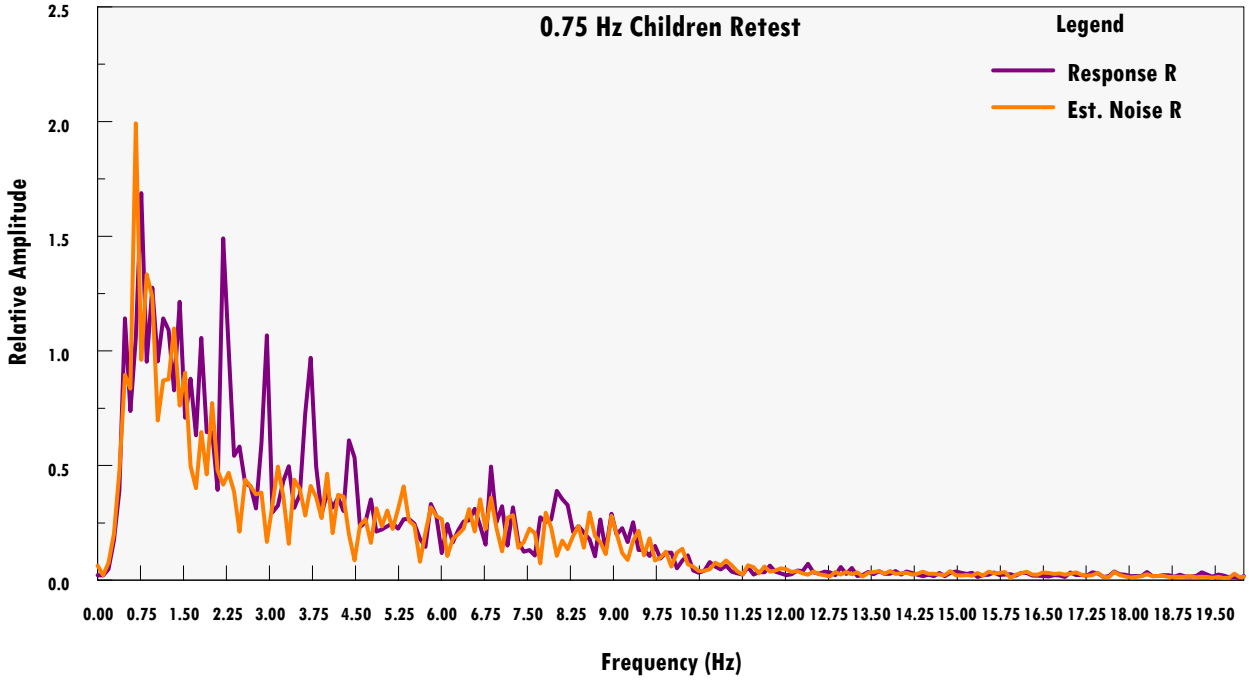


Figure 46 Spectral between-test session reliability adults awake

5.3.2.2 Children

The within-test session accuracy at 0.75 Hz (Figure 47) revealed a series of spectral components at integer multiples of the fundamental frequency that corresponded to those revealed in the original test. In addition, the relative amplitude of the response decreased while the level of background noise increased; thus, there were fewer spectral components that were clearly discernible from the estimated background noise in the retest, compared to the original test. There were 10 spectral components identified compared to 12 components in the original test. Like the original test results, the averaged response of the retest also demonstrated a redistribution of power in the spectrum. This new distribution of power repositioned the integer that demonstrated the highest amplitude from the third harmonic (2.25 Hz) for the original test to the fundamental frequency in the retest. In addition, the integer that demonstrated the lowest amplitude shifted from the 15^{th} harmonic (11.25 Hz) for the original test to the 10^{th} harmonic (9.75 Hz) in the retest.



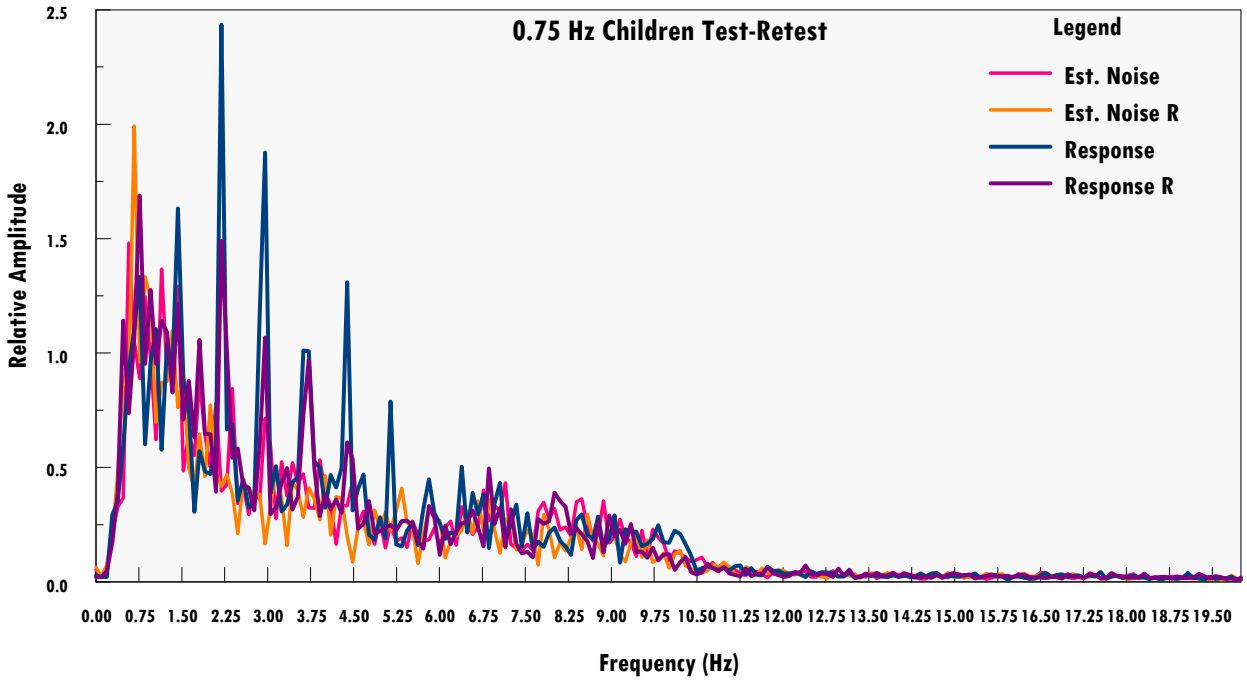


Figure 47 Spectral within-test session reliability in children

Pearson's product-moment correlation coefficients were computed to assess overall consistency and stability of within-test session response measurements for children. A strong positive correlation was found (r (12) = .737, p = .006), indicating a significant linear relationship in the within-test session accuracy at 0.75 Hz. In addition, the ICC was performed to quantify the proportion of the variance in responses that can be attributed to "true" variation among individuals. It was found that the ICC (2, 1) = .645, p = .004 at 0.75 Hz, indicating that good agreement at 0.75 Hz.

5.4 ADULTS ASLEEP

Specific Aim 2: Explore the effects of repetition (modulation) rate (frequency) on response amplitude during sleep, to (a) demonstrate if effects differ from those obtained when adult subjects were awake.

5.4.1 Temporal analysis of quasi-steady-state responses

Grand averages of the ASSR waveforms at various modulation frequencies while adults were in natural sleep are shown in Figures 48 through 51. These figures depict the time domain over the same two response capture windows at each modulation frequency. For direct comparison, waveforms for both adults awake (black) and during sleep (red) have been superimposed in each of the representative figures.

At the modulation frequencies of 0.75 through 2.5 Hz, larger averaged responses were observed in adults during sleep, compared to adults tested while awake. Scrutiny of the first 1000 msec (Figure. 48B) reveals what appears to be the P_1-N_1-P_2 complex, strongly reminiscent of the conventionally-tested transient-response. However, when the modulation frequency was increased to 2.5 Hz, the individual response components are difficult discern in the full frame (Figure 49A), but remain vivid in the shorter-window view (B). Like the adult response while awake, the amplitude of the averaged waveform at 2.5 Hz was considerably decreased for all components during sleep. Although qualitatively similar, it is not clear that this waveform literally represents the LLR.

Increasing the modulation frequency to 5 Hz, even in the time-expanded view (Figure 49B); the averaged waveform morphology no longer bore any resemblance to the P_1-N_1-P_2. Similar to the averaged waveform in adults while awake, a closer assessment at the onset of the response train at 10 Hz (Figure 50B) reveals something like the P_1-N_1-P_2 complex. When the modulation frequency was increased to 20 Hz, the amplitude of the response actually increases substantially compared to that at 10 Hz. In addition, the amplitude of the averaged waveform was nearly identical to that observed in the adult response while awake.

At modulation frequencies of 40 and 80 Hz, responses appear as virtually continuous quasi-sinusoidal signals following the modulation frequency throughout the capture window of 1000 msec (Figure 51AB). When the modulation frequency was increased to 40 Hz the amplitude of the averaged waveform decreased slightly, whereas the amplitude of the averaged waveform at 80 Hz was virtually the same in the adult response while awake.

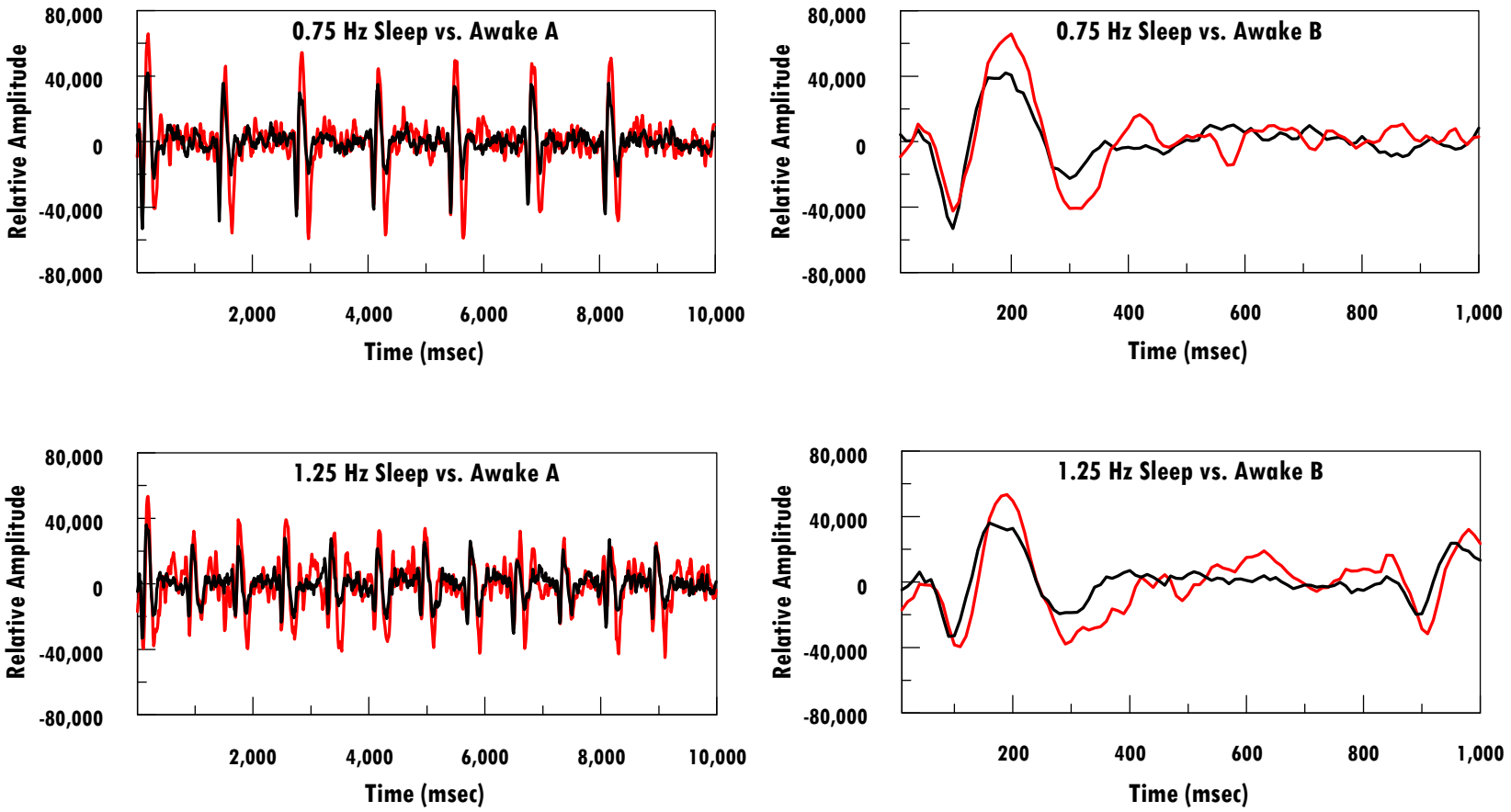


Figure 48 Grand averages at 0.75 and 1.25 Hz during sleep (red)

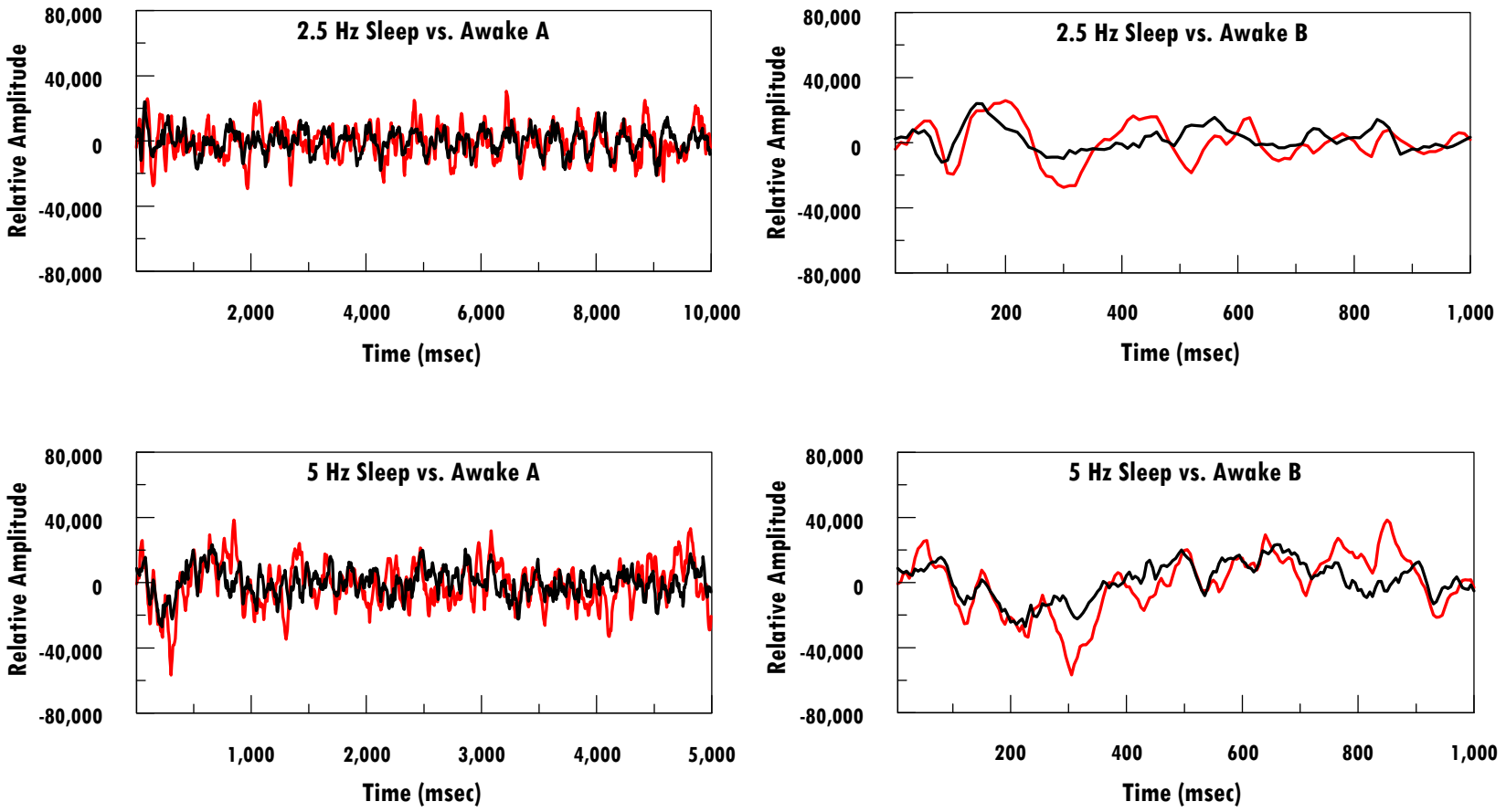


Figure 49 Grand averages at 2.5 and 5 Hz during sleep (red)

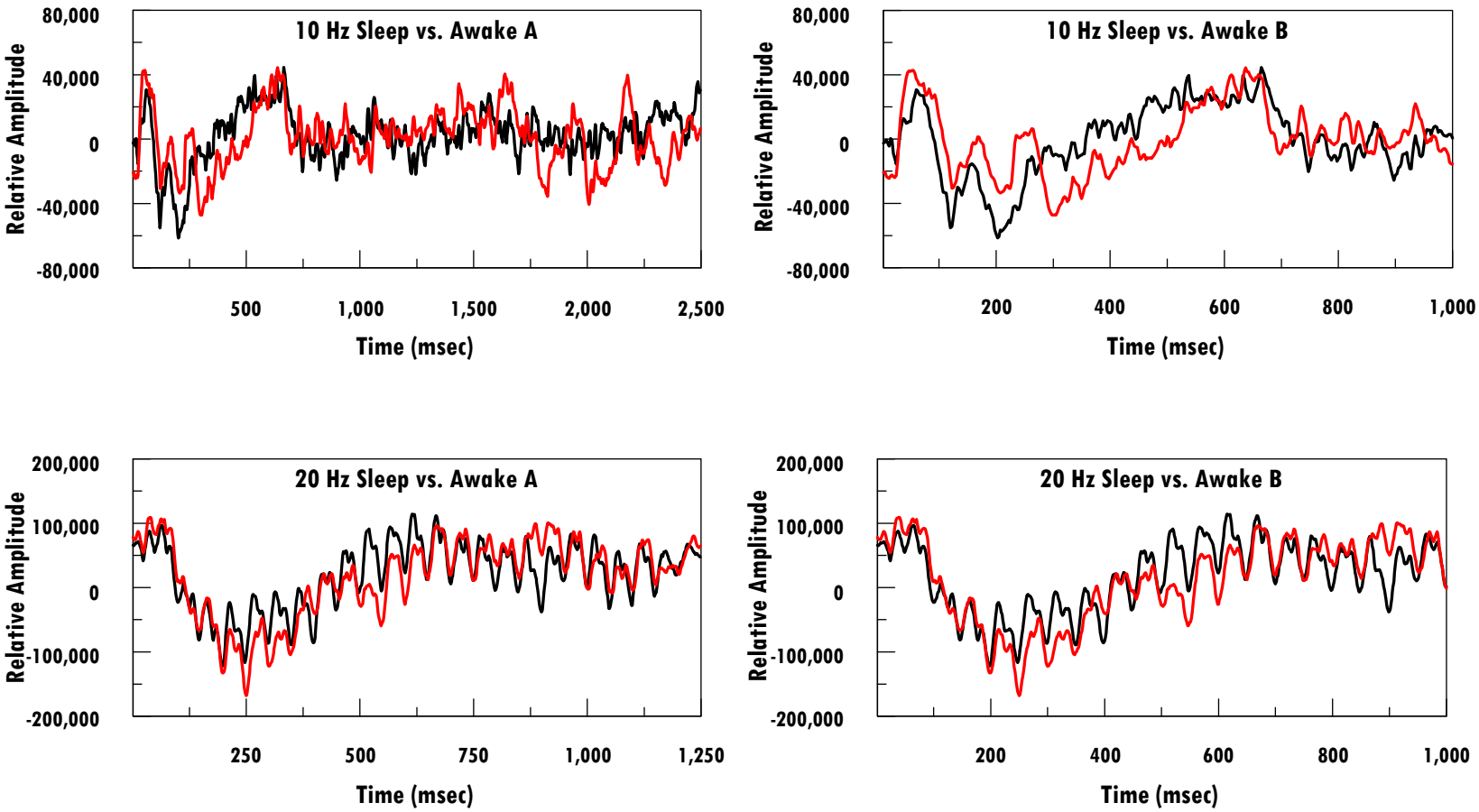


Figure 50 Grand averages at 10 and 20 Hz during sleep (red)

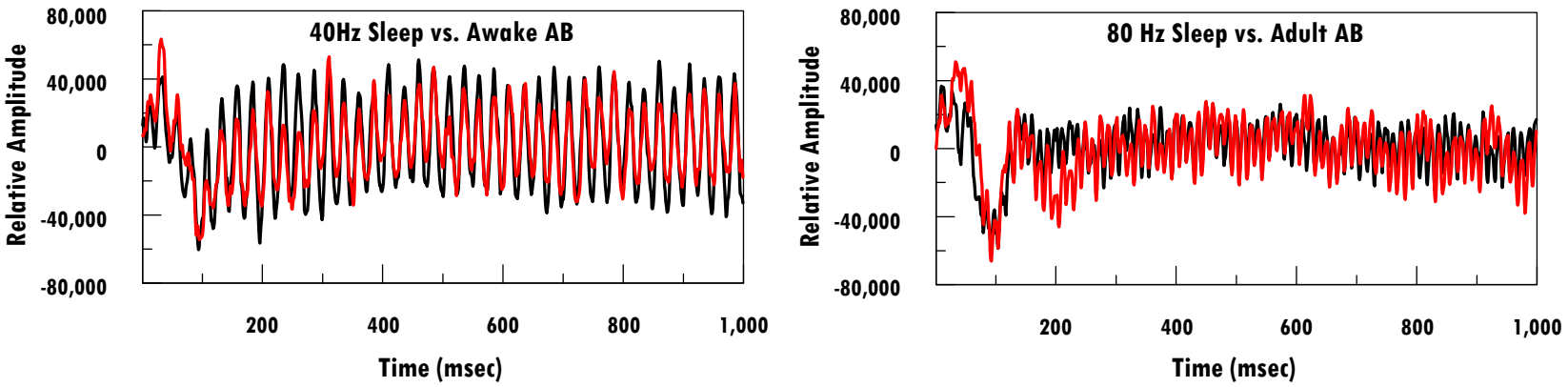


Figure 51 Grand averages at 40 and 80 Hz during sleep (red)

5.4.2 Spectral analysis of quasi-steady-state responses

Grand averages of the ASSR power spectra at various modulation frequencies while adults were in natural sleep are shown in Figures 52 through 59. Similarly, the total response and the estimated background noise for adults during sleep and when adults were tested while awake have been superimposed in each of the representative figures.

When F1=0.75 Hz, the averaged steady-state response was represented by a series of spectral components at integer multiples of the fundamental frequency that corresponded to those revealed in adult responses while awake. The averaged response obtained during sleep was substantially larger than in adults tested while awake. There were 12 spectral components that were identified during sleep, compared to 16 components observed while awake. However, during sleep the averaged response demonstrated a redistribution of power in the spectrum, such that, the power of the response was shifted toward the lower harmonics. Thus, of the 12 spectral components identified during sleep, the power remained at the sixth harmonic (4.5 Hz); however, the integer that demonstrated the lowest power was repositioned from the 16^{th} harmonic (12 Hz) for adults while awake to the 15^{th} harmonic (11.25 Hz) in adults during sleep.

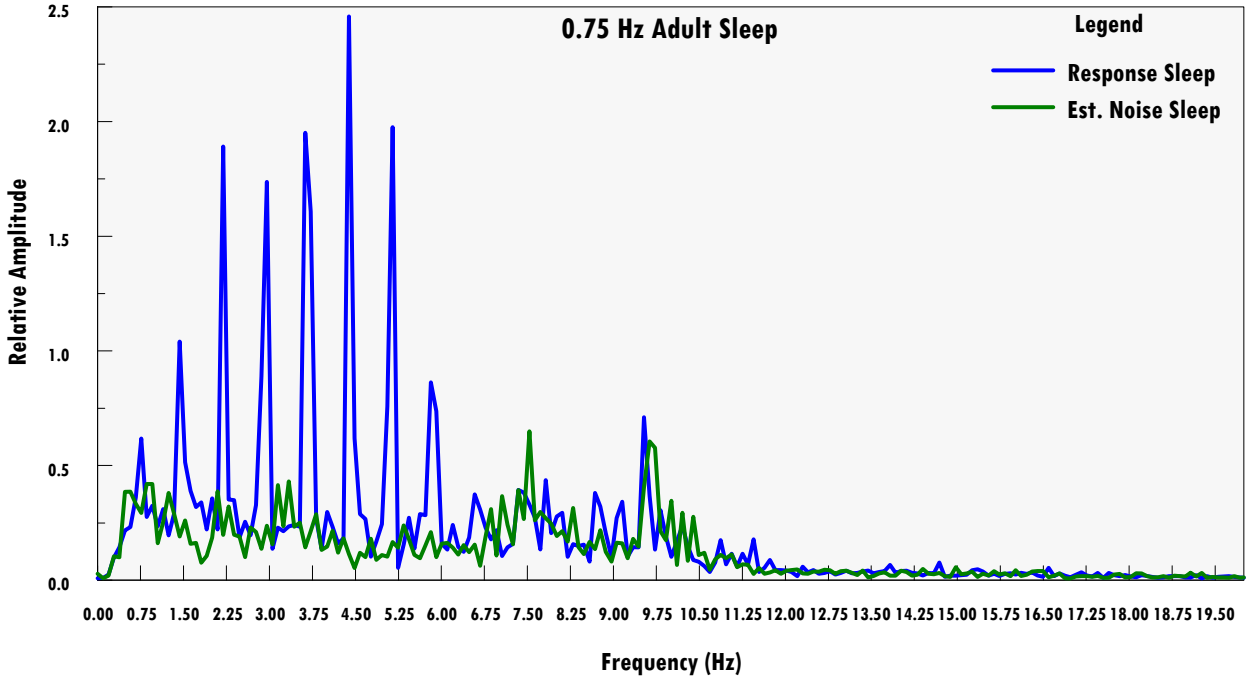
Likewise, when F1=1.25 Hz, the averaged steady-state response was represented by several components that were harmonically related in and around the fundamental frequency that corresponded to those revealed in adult responses while awake. The averaged response at 1.25 Hz was substantially larger in adults during sleep than in adults tested while awake. Like the response observed in adults while awake, there were 12 spectral components that were identified during sleep. Similar to the redistribution of power in the spectrum at 0.75 Hz, the power of the response at 1.25 Hz shifted toward the lower harmonics. Thus, of the 12 spectral components

identified, the highest power shifted from fourth harmonic (5 Hz) for adults while awake, to the third harmonic (3.75 Hz) in adults during sleep; however, the integer that demonstrated the lowest power remained at the 12th harmonic (15 Hz).

Similarly, when F1=2.5 Hz, the averaged steady-state response was represented by a series of spectral components at integer multiples of the fundamental frequency that corresponded to those revealed in adult responses while awake. The averaged response at 2.5 Hz was considerably larger in adults during sleep compared to adult responses observed while awake. Like the response observed in adults while awake, there were six spectral components that were identified during sleep. Of the six components identified, the highest power remained at the fundamental frequency; however, the integer that demonstrated the lowest power shifted somewhat from the seventh harmonic (17.5 Hz) for adults while awake, to the sixth harmonic (15 Hz) in adults during sleep.

Likewise, when F1=5, 10, and 20 Hz, the averaged responses of each were represented by several components that were harmonically related in and around the fundamental frequency that corresponded to those revealed in adult responses while awake. Unlike the three lowest modulation frequencies, the spectral content of the response during sleep at 5, 10 and 20 Hz revealed trends that matched those observed at corresponding modulation frequencies in adults tested while awake. Even so, the averaged responses obtained at 5 and 10 Hz were slightly larger in adults during sleep than adults while awake. Conversely, averaged responses obtained at 20 Hz were considerably smaller in adults during sleep compared to adult responses observed while awake. When F1=40 and 80 Hz the spectral content of the response during sleep revealed trends that were identical to those observed at corresponding modulation frequencies in adults tested while awake. However, the averaged response obtained at 40 Hz was considerably

smaller when measured at the fundamental frequency during sleep than when adults were tested while awake.



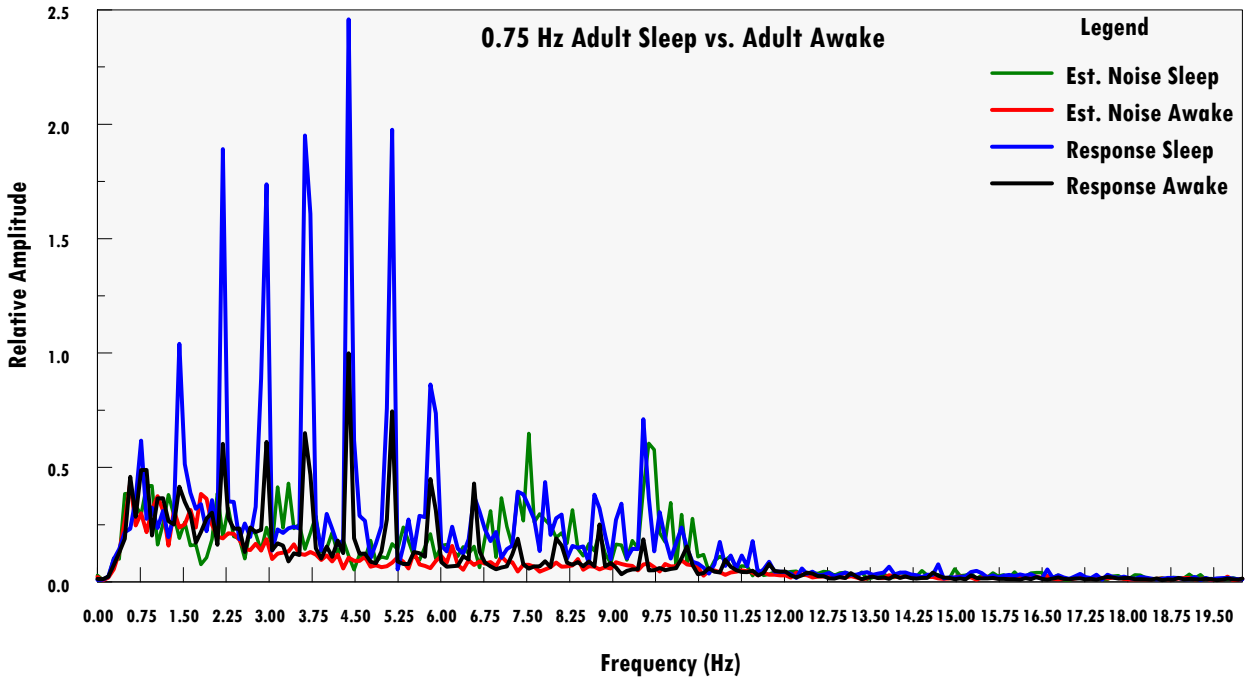
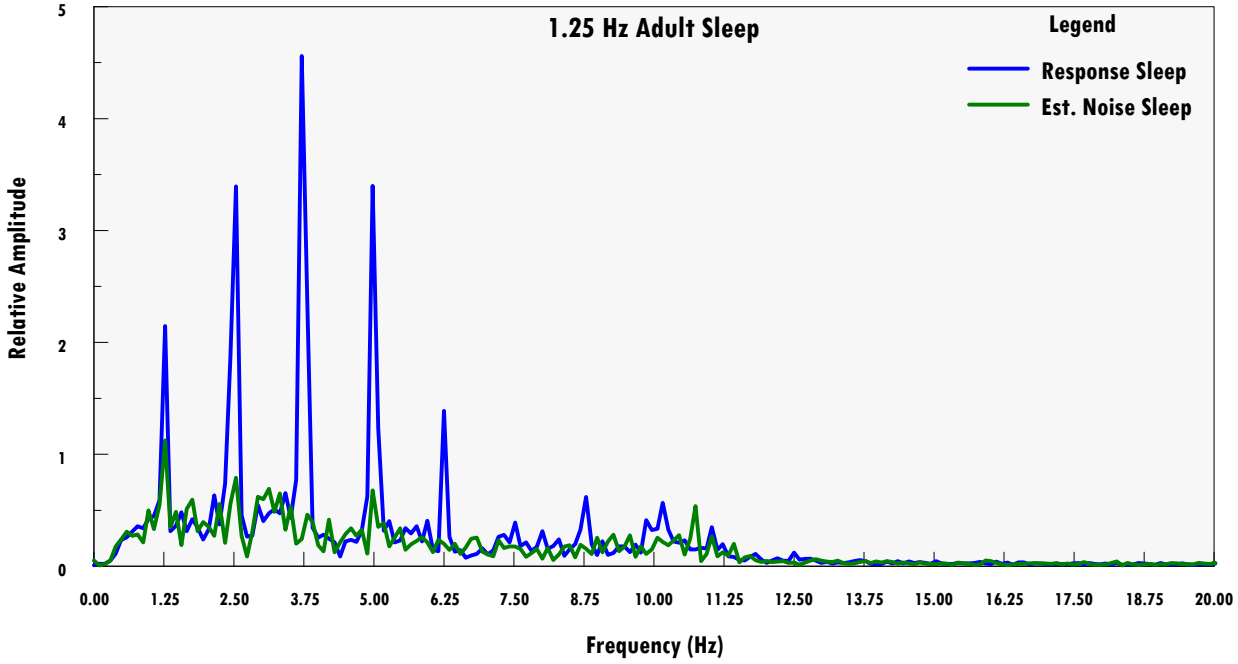


Figure 52 Grand averages at 0.75 Hz during sleep and comparison



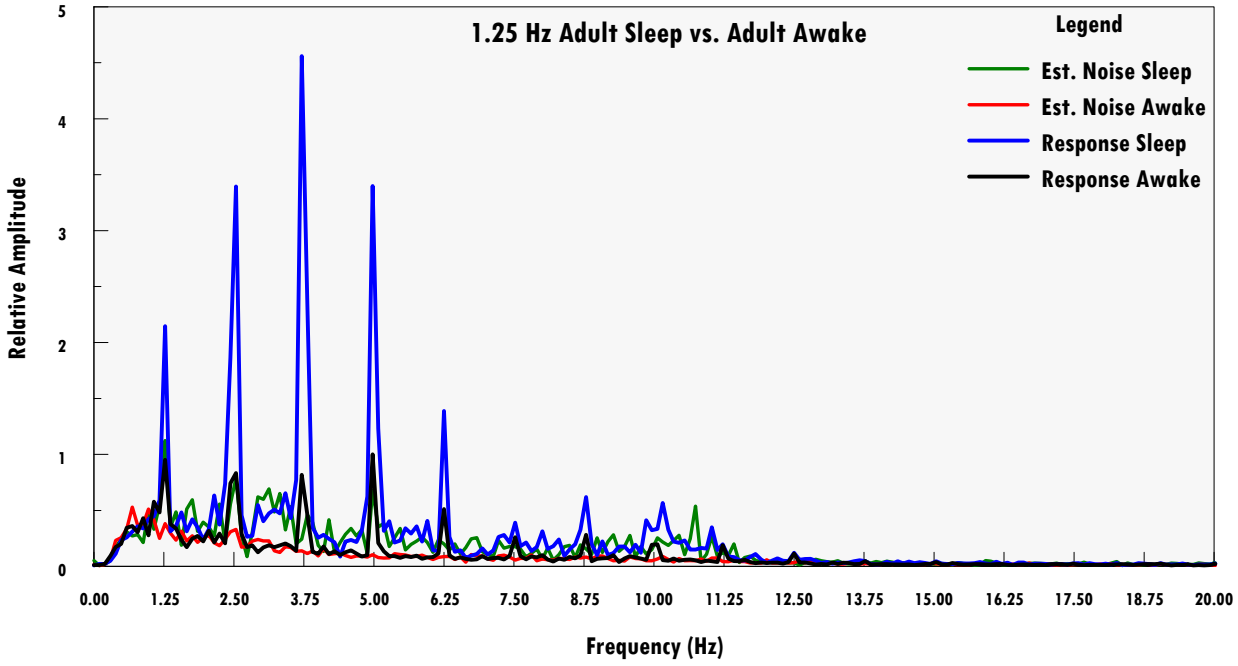
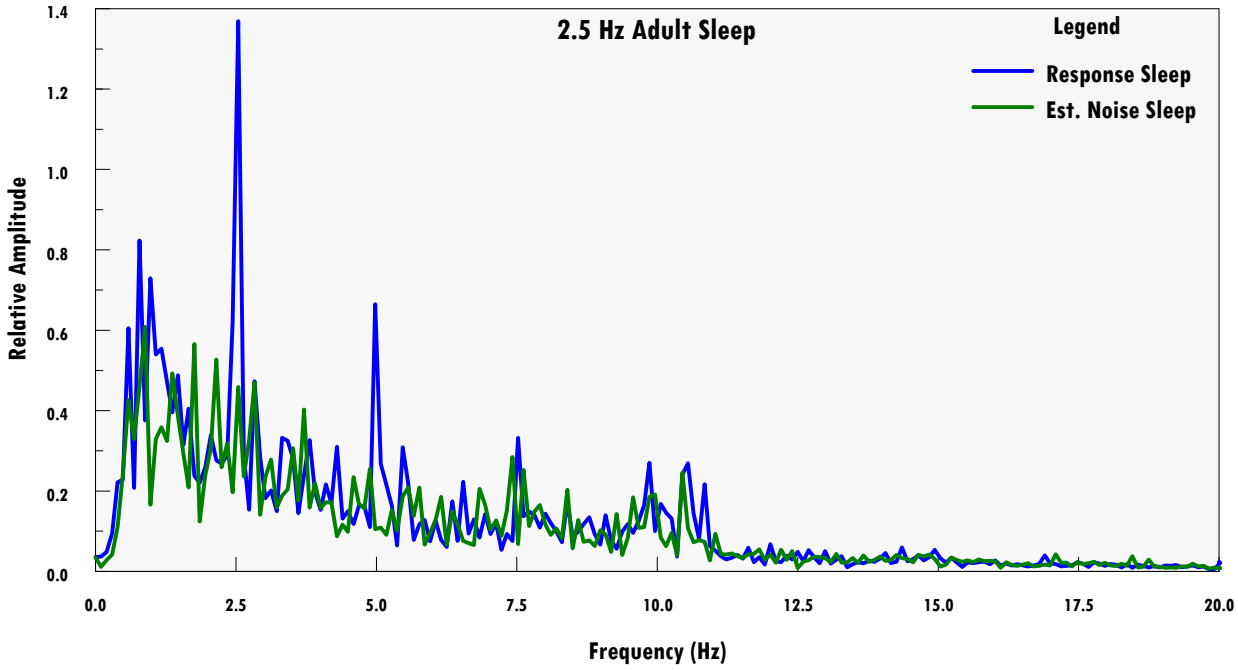


Figure 53 Grand averages at 1.25 Hz during sleep and comparison



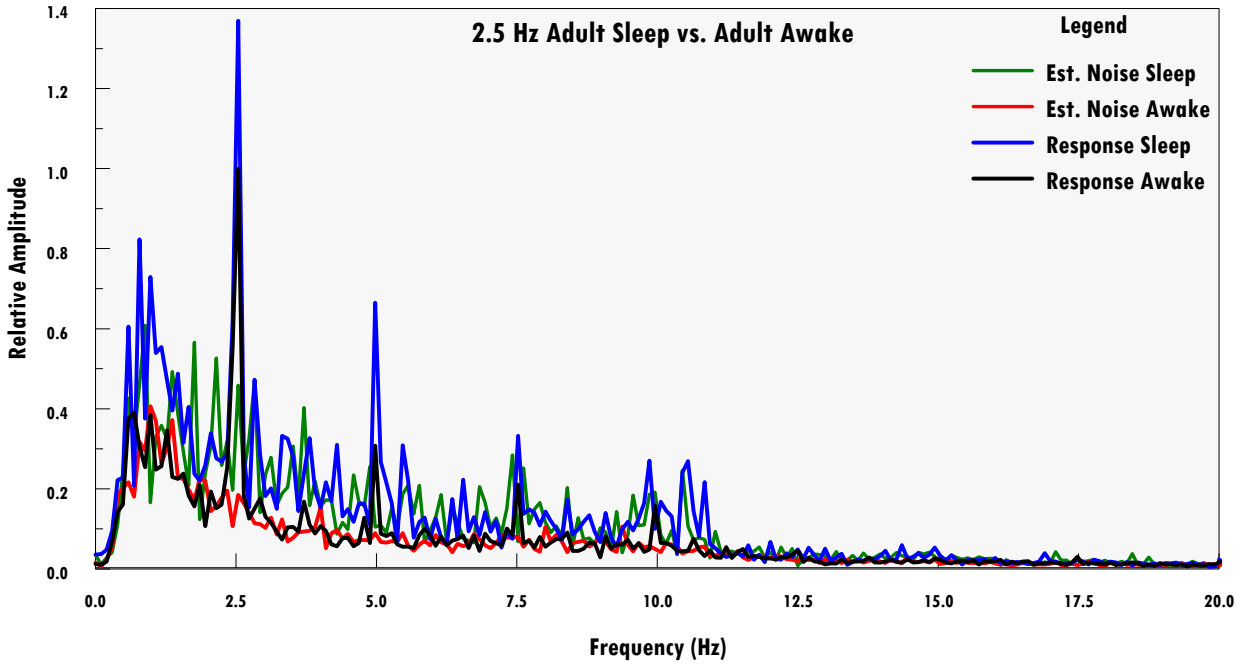
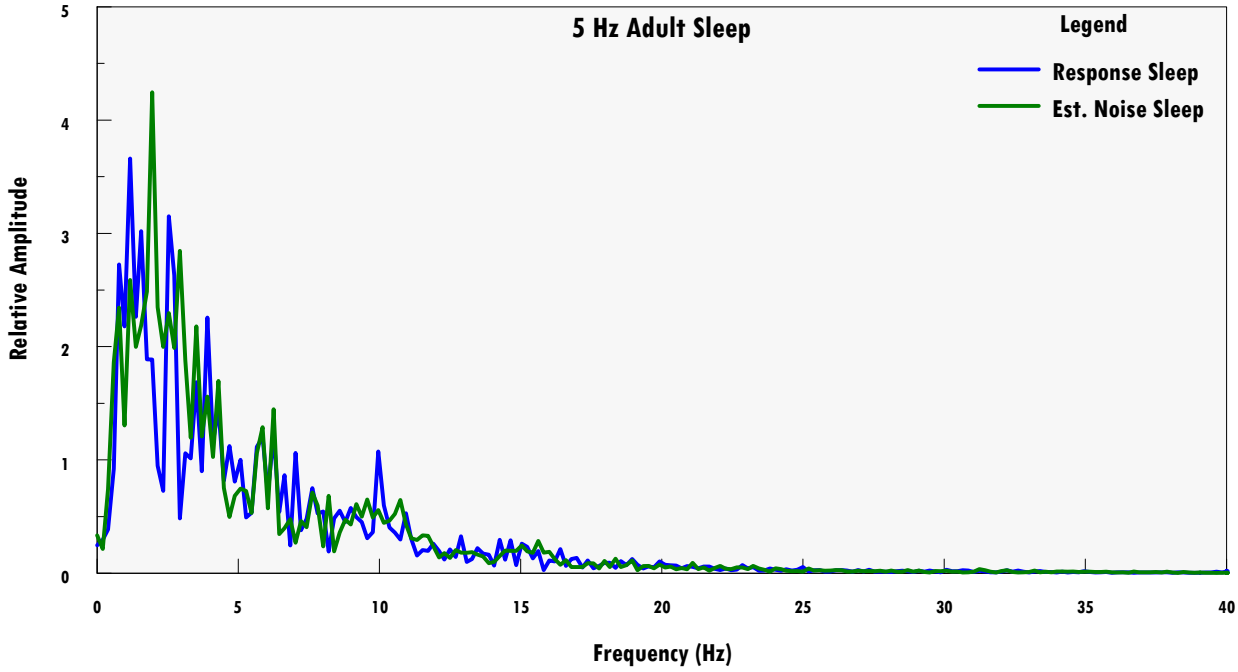


Figure 54 Grand averages at 2.5 Hz during sleep and comparison



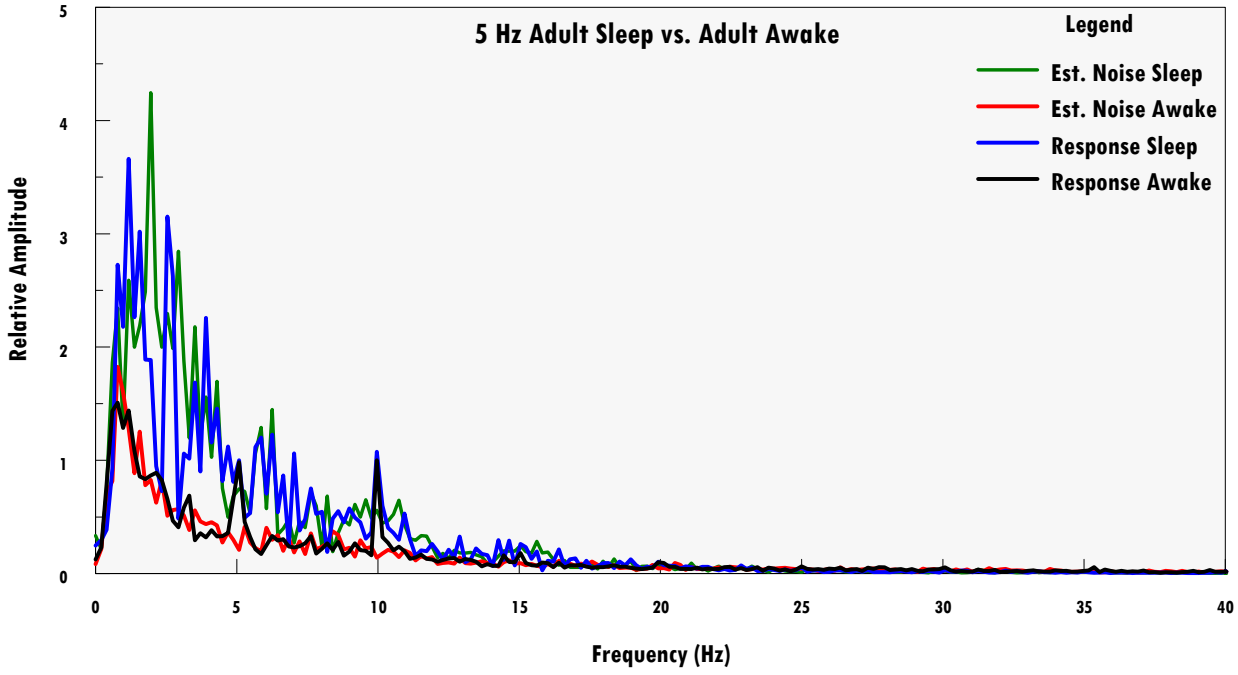
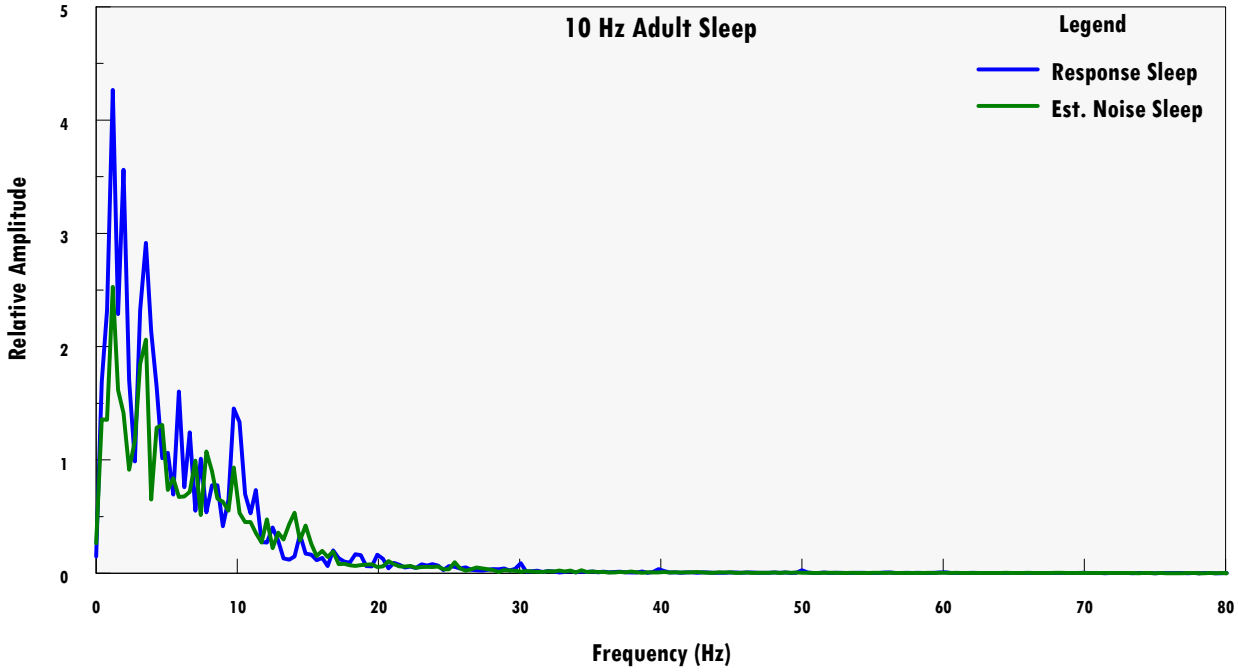


Figure 55 Grand averages at 5 Hz during sleep and comparison



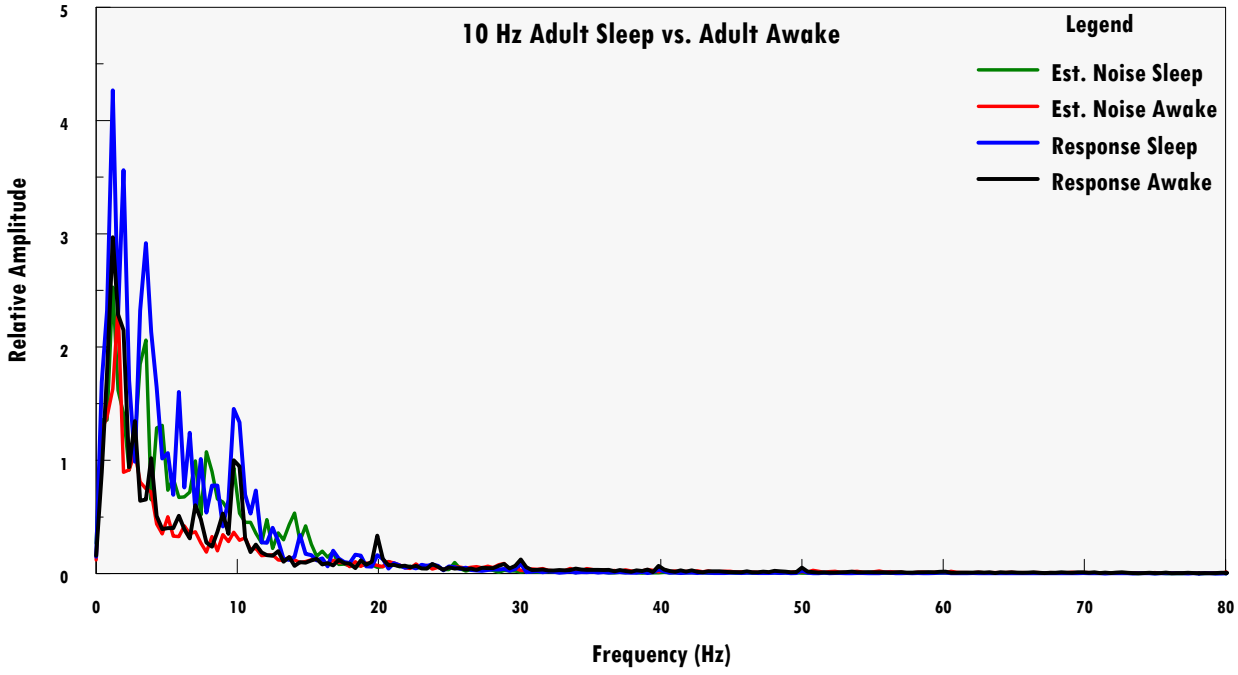


Figure 56 Grand averages at 10 Hz during sleep and comparison

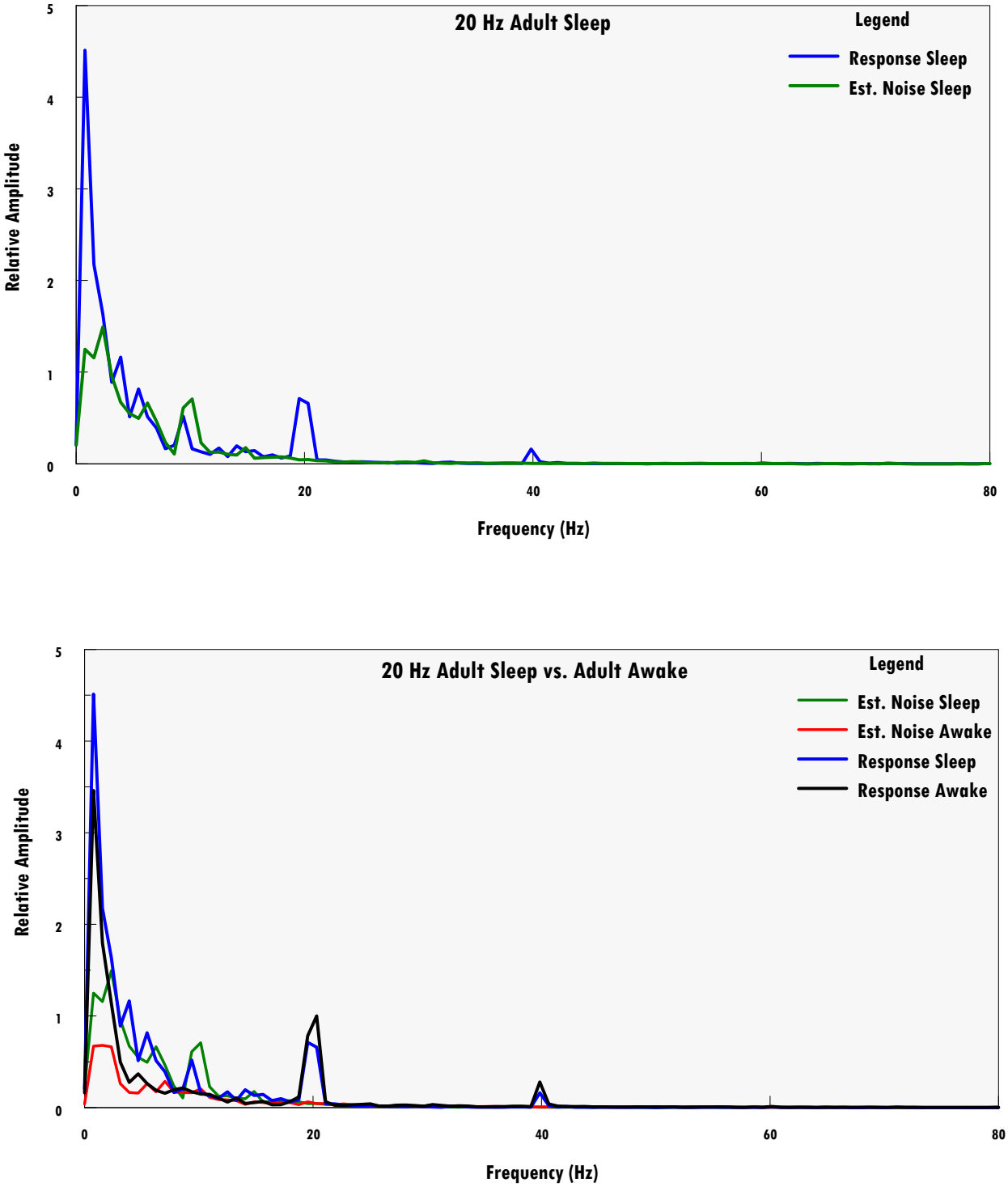
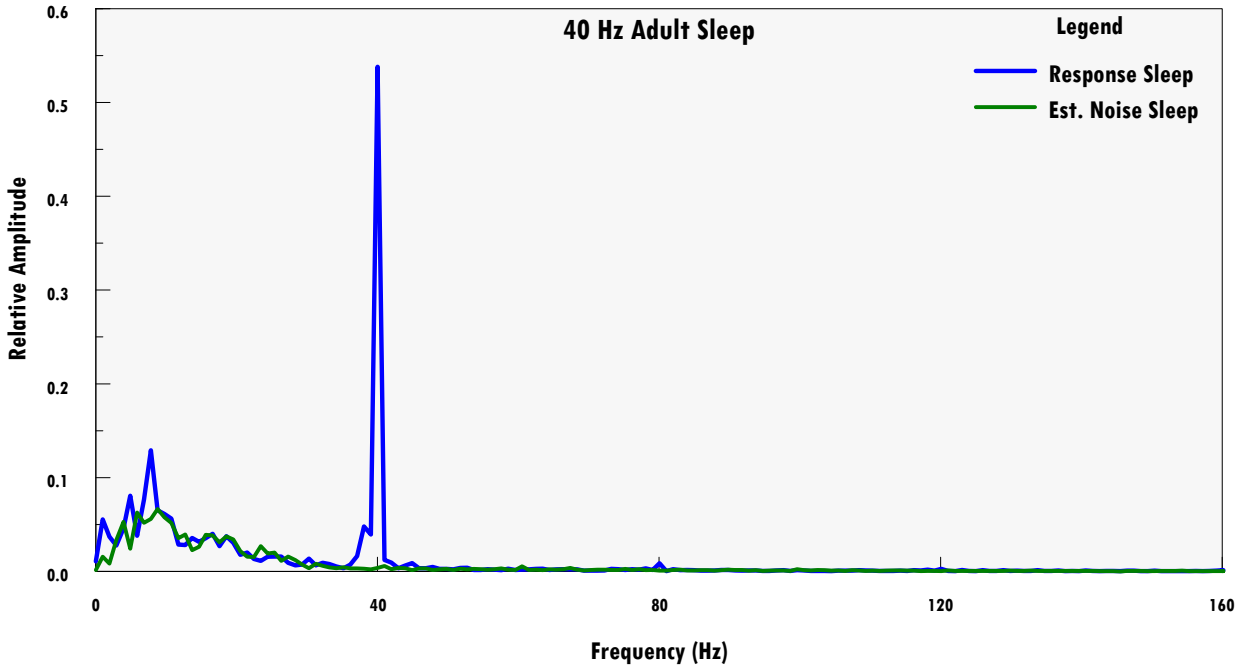


Figure 57 Grand averages at 20 Hz during sleep and comparison



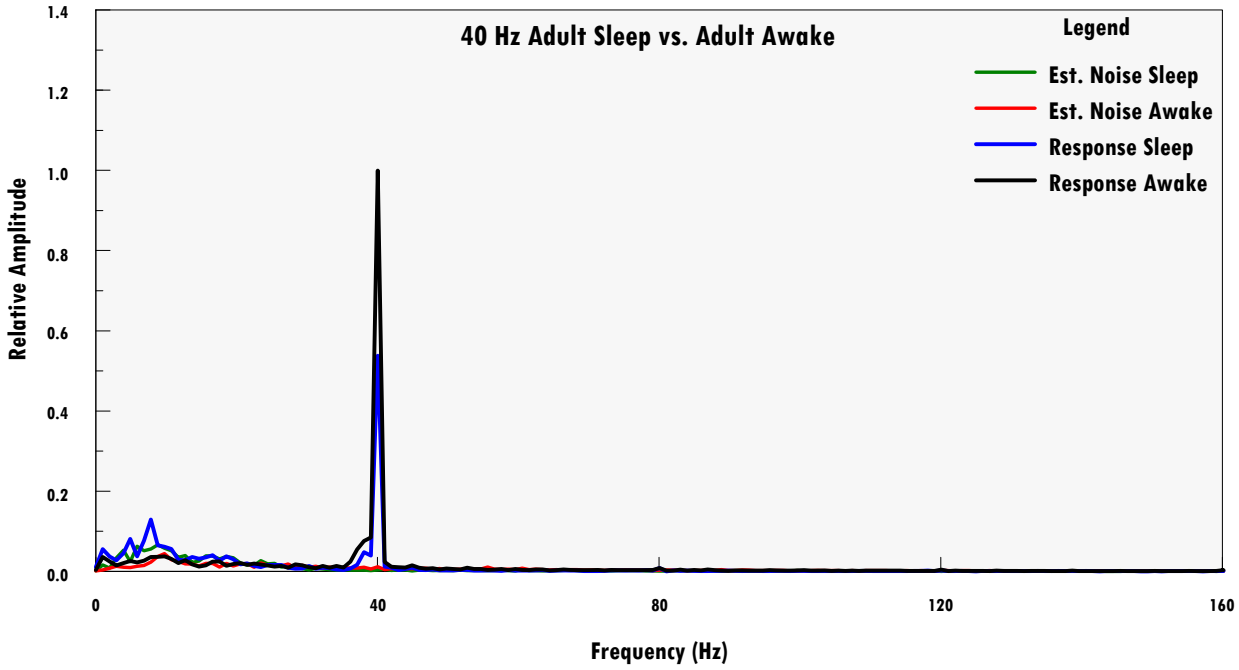
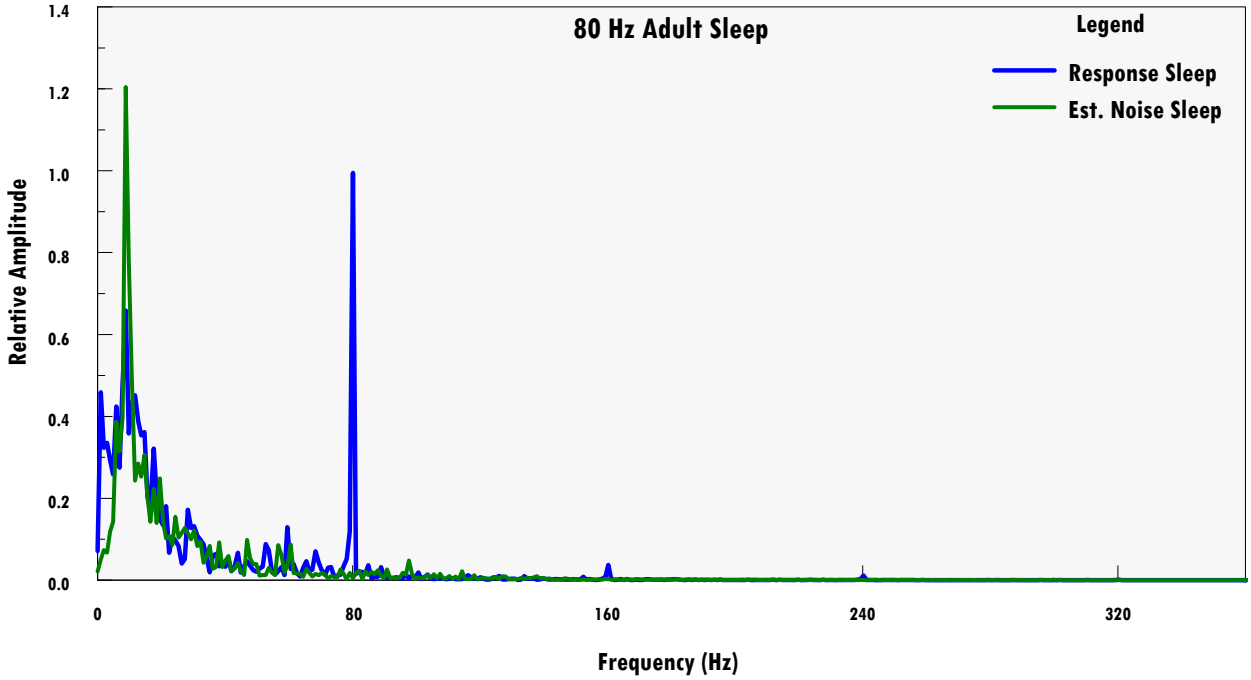


Figure 58 Grand averages at 40 Hz during sleep and comparison



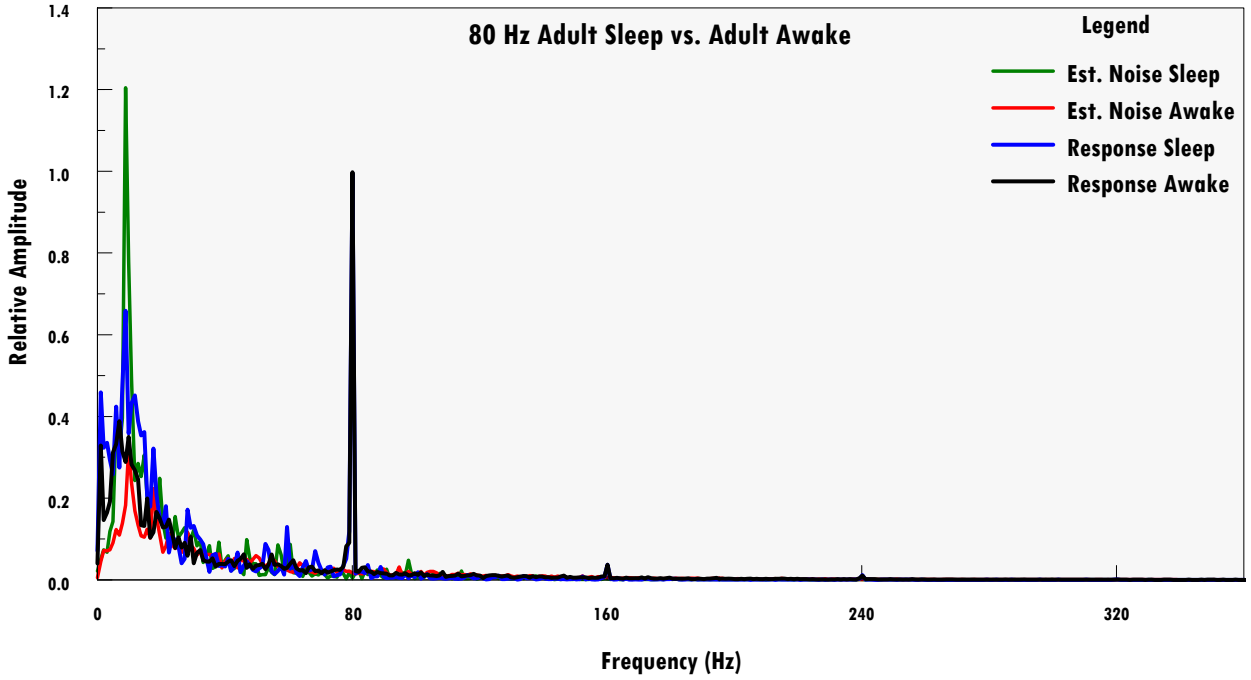
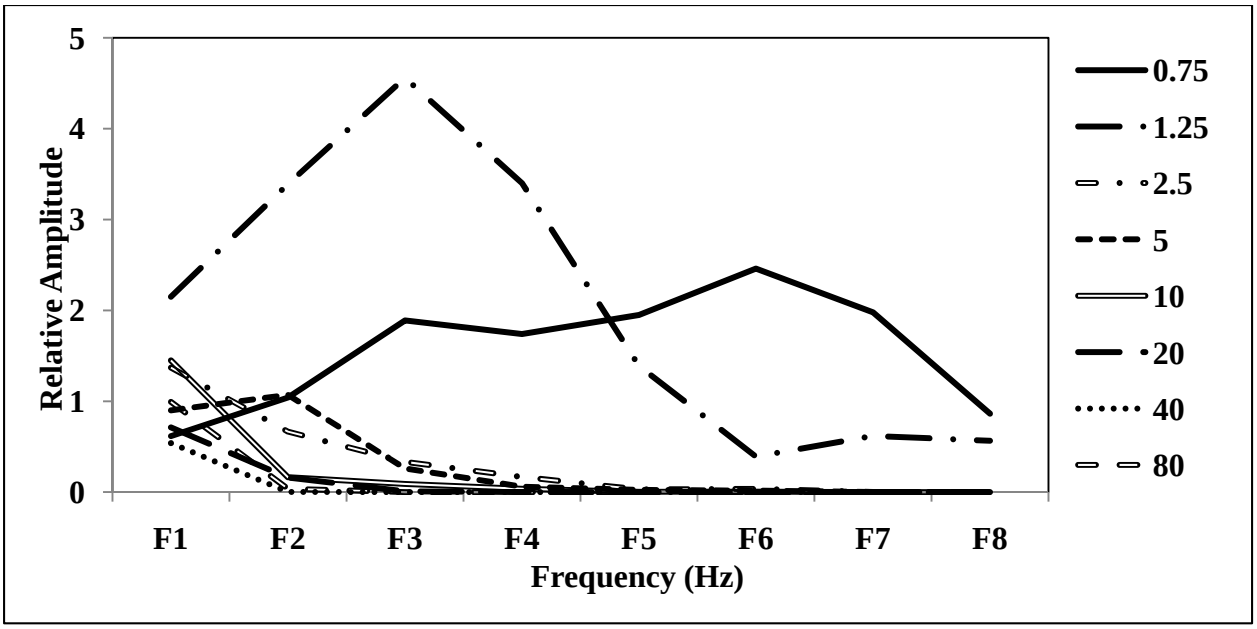


Figure 59 Grand averages at 80 Hz during sleep and comparison

Examination of the first eight harmonics from each spectrum well reflects the harmonic structure of the averaged responses across modulation frequency during sleep (Figure 60). The overall structure illustrates that the number of harmonically related frequency components that were identified decreased as modulation frequency increased from 0.75 to 80 Hz. In addition, the power of the spectra was highest at the sixth harmonic at 0.75 and the third harmonic at 1.25 Hz, whereas, the power of the spectra was highest at the fundamental frequency at modulation frequencies from 2.5 and above. A closer inspection of the averaged responses when adults were awake (black) compared to when adults were asleep (red) at modulation frequencies of less than 10 Hz, revealed substantial differences in the relative amplitudes of the responses at 0.75 and 1.25 Hz. No other appreciable differences were observed for responses obtained at 2.5 through 10 Hz.



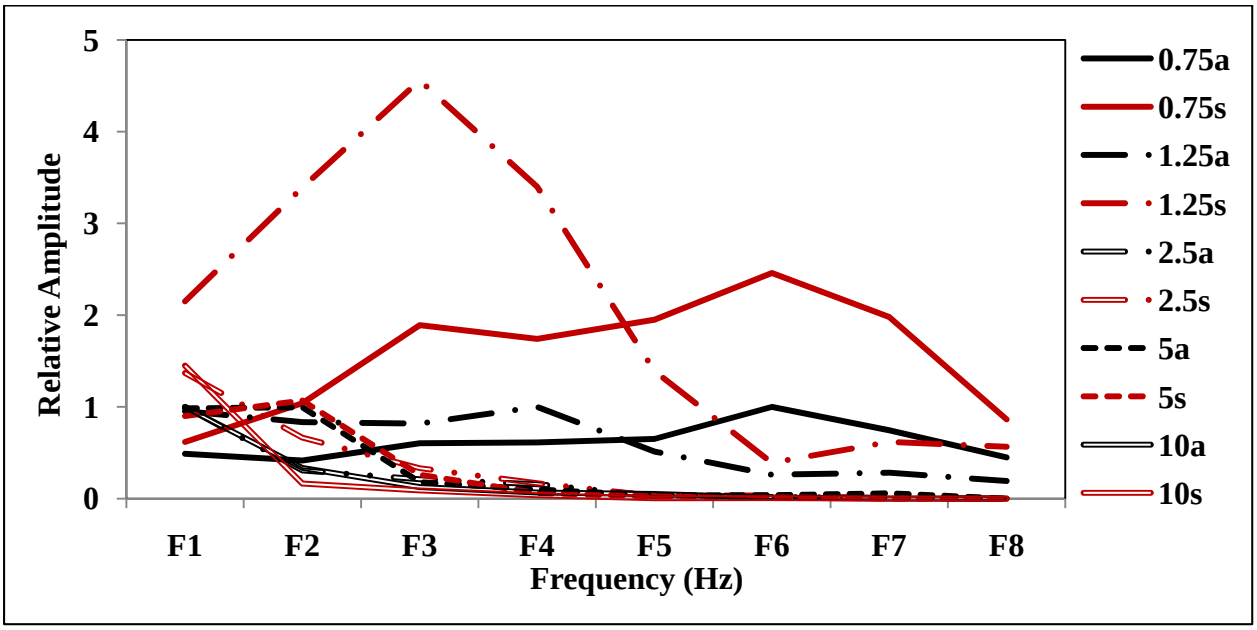


Figure 60 Harmonic structure adults during sleep

In addition, an analysis of the harmonic sum of the response (Figure 61) reveals trends that were similar to those observed in adults. Namely, the overall relative amplitude of the response decreased as modulation frequency increased from 0.75 to 80 Hz. In addition, when the harmonic sum of the response for adults tested during sleep (red) and tested while awake (black) were superimposed, notable differences were seen at the modulation extremes. Substantial differences were seen at 0.75 and 1.25 Hz; in which harmonic sum was larger for adults during sleep compared to adults awake. Likewise, differences were seen at 20 and 40 Hz, in which the harmonic sum was smaller for adults during sleep compared to adults awake. No appreciable differences were observed between the two groups at 5, 10 and 80 Hz.

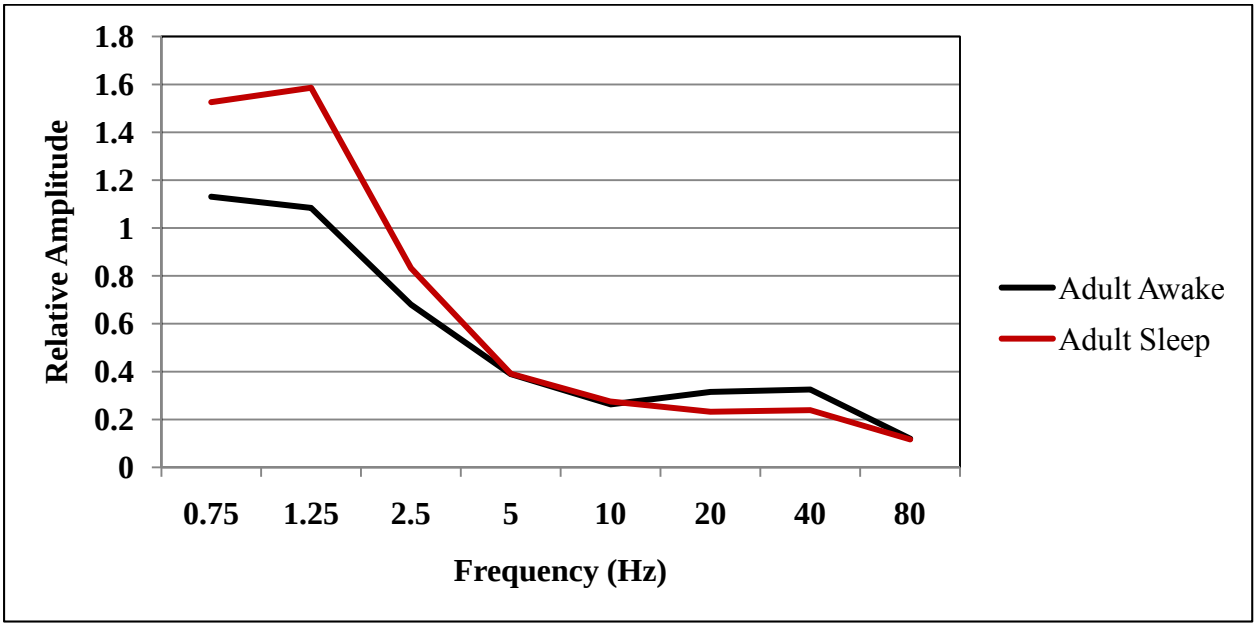


Figure 61 Harmonic sum adults during sleep

Specific Aim 2: Explore the effects of repetition (modulation) rate (frequency) on response amplitude during sleep to (b) identify the repetition rate(s) which evoke(s) the maximal response amplitude.

Moreover, as an exploratory examination, it was originally proposed to perform a two-way ANOVA (subject state by repetition rate) to test whether state of arousal (awake versus asleep) had an effect on the response amplitude of adults when stimuli were presented at different repetition rates. However, the sample sizes for each group, awake versus asleep, were not equal. Thus, we conducted a paired samples t-test to compare the responses of adults when awake and when asleep at selected repetition rates. Since response amplitudes for modulation frequencies greater than 10 Hz can be predicted from results of previous AEP studies, a paired samples t-test was conducted to specifically compare the amplitude differences among the age and arousal groups on the repetition rates of 10 Hz and less. Table 28 shows the means and SDs for adults awake and asleep across modulation frequencies. Results revealed that the mean response for adults during sleep was significantly higher than the mean response for adults awake 0.75 Hz (t = -4.577, p = .001) and at 1.25 Hz (t = -2.296, p = .042).

Table 28 Means and SDs for Adults Awake and During Sleep

Frequency	Group	Means	SD
0.75	Awake	1.19E-06	3.19E-07
	Sleep	1.71E-06	4.72E-07
1.25	Awake	1.05E-06	2.13E-07
	Sleep	1.62E-06	9.24E-07
2.5	Awake	7.18E-07	2.56E-07
	Sleep	8.33E-07	2.53E-07
5	Awake	3.76E-07	9.29E-08
	Sleep	3.91E-07	1.86E-07
10	Awake	2.54E-07	5.59E-08
	Sleep	2.75E-07	1.76E-07

Specific Aim 2: Explore the effects of repetition (modulation) rate (frequency) on response amplitude during sleep to (c) demonstrate overall consistency and stability of response measurements between the two states of arousal in adults.

Pearson's product-moment correlation coefficients were planned originally to determine the strength of the linear trend between responses at the two states of arousal (awake versus asleep) at each repetition rate. However, three outliers were identified in our data. Because Pearson's correlation is sensitive to outliers, especially with small sample sizes, we calculated Spearman rank-order correlation coefficient. Moderate-to-strong positive Spearman correlations that were significant were found at 0.75 Hz (*rho* (11) = .670, p = .012) and at 1.25 Hz (*rho* (10) = .671, p = .017), indicating fairly good consistency between responses while adults were awake and while adults were asleep. Likewise, a moderate positive correlation that was significant was found at 20 Hz (*rho* (10) = .629, p = .028), indicating a moderate degree of consistency between responses while adults were awake and while adults were asleep. Similarly, strong positive correlations that were significant were found at 40 Hz (*rho* (11) = .907, p < .001) and at 80 Hz

(*rho* (10) = .923, $p < .001$), indicating very high degree of consistency between responses while adults were awake and while adults were asleep. Small and non-significant correlations were found at 2.5, 5 and 10 Hz.

5.5 GROUP DATA ANALYSES

Specific Aim 3: Examine the use of the fundamental as well as substantially higher harmonics, at each rate of repetition (modulation frequency) to determine if each analysis provides improved stability of response measurement.

5.5.1 Adults

Figure 62 shows the relative amplitude as a function of the two different analyses for adults. For the analysis based on the harmonic sum, the relative amplitude was largest between 0.75 and 1.25 Hz and smallest at 10 and 80 Hz. Above 1.25 Hz, the relative amplitude decreased with increasing modulation frequency. Maximum responses occurred at 0.75 and 40 Hz. Conversely, for the analysis based on the fundamental frequency, the relative amplitudes were largest between 2.5 and 80 Hz, and the smallest between 0.75 and 1.25 Hz. Below 2.5 Hz, the relative amplitude increased with increasing modulation frequency, then reached an asymptote when the modulation frequency was increased to 2.5 Hz.

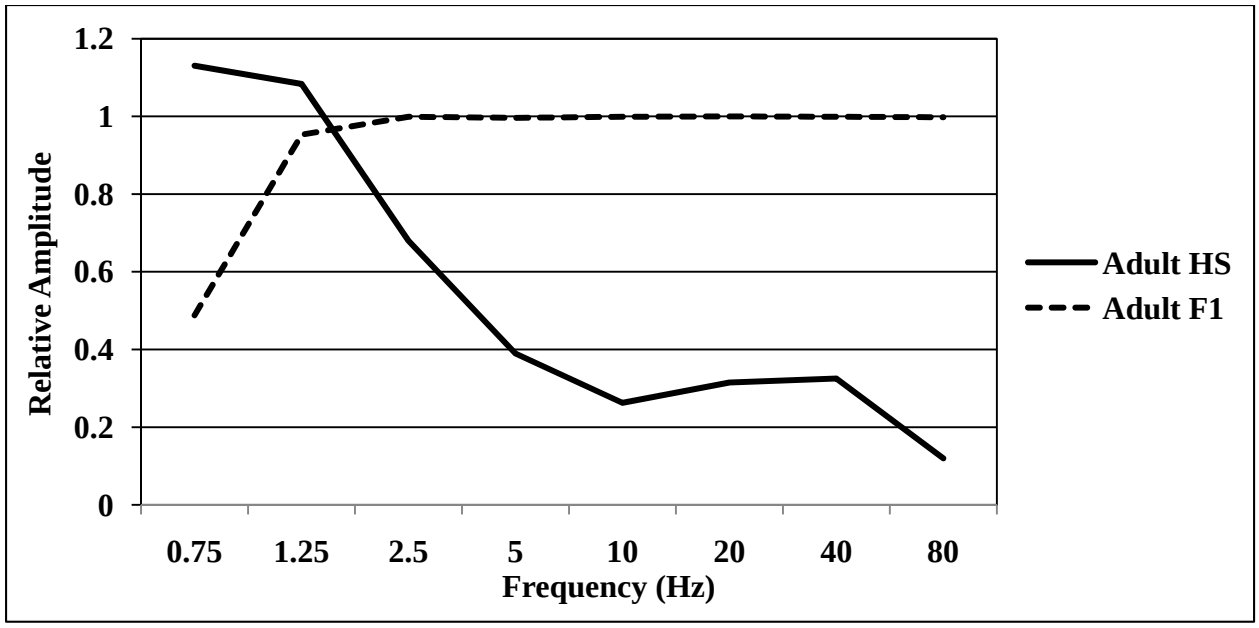


Figure 62 Harmonic sums vs. fundamental adults

5.5.2 Children

Figure 63 shows the relative amplitude as a function of the two different analyses for children. For the analysis based on the harmonic sum, the relative amplitude was largest between 0.75 and 1.25 Hz, and the smallest at 80 Hz. Above 1.25 Hz, the relative amplitude decreased with increasing modulation frequency. Conversely, for the analysis based on the fundamental frequency, the relative amplitude was largest at 5 Hz, and smallest at 0.75 and 40 Hz. Below 5 Hz, the relative amplitude increased with increasing modulation frequency, whereas above 5 Hz just the opposite occurred, the relative amplitude of the response decreased with increasing modulation frequency.

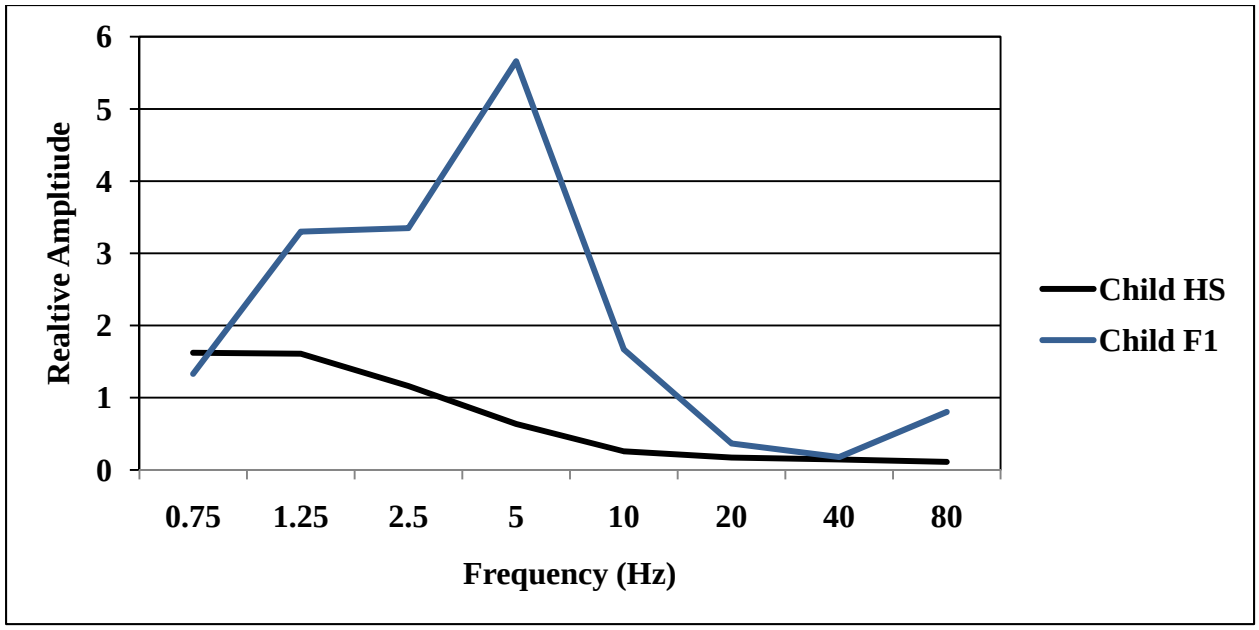


Figure 63 Harmonic sums vs. fundamental children

5.5.3 Adults sleep

Figure 64 shows the relative amplitude as a function of the two different analyses for adults tested during sleep. For the analysis based on the harmonic sum, the relative amplitude was largest at 1.25 Hz, and smallest at 80 Hz. Above 1.25 Hz, the relative amplitude decreased with increasing modulation frequency. Maximum responses occurred at 1.25 and 40 Hz. Conversely, for the analysis based on the fundamental frequency, the relative amplitudes were largest at 1.25, 10 and 80 Hz, and smallest at 0.75, 5 and 40 Hz.

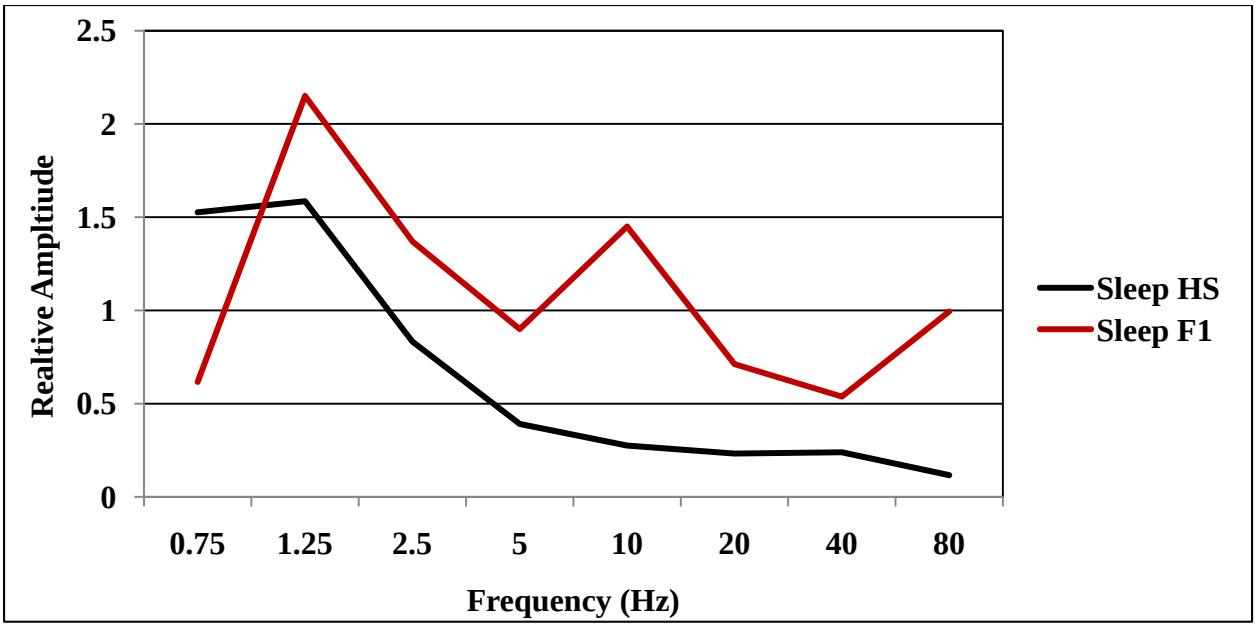


Figure 64 Harmonic sums vs. fundamental adults during sleep

6.0 DISCUSSION

6.1 TEMPORAL ANALYSIS

6.1.1 Analysis of transient AEP responses

Transient AEPs in the three major time ranges (LLR, MLR, and ABR) were detected in all adults and children. These responses served as bases of comparisons via conventional methods across conditions and groups and between the findings for this investigation and results available in the literature, including those characterizing the maturation of the auditory cortical function in children. Moreover, they functioned as a backdrop for the analysis and interpretation of the steady-state responses.

With respect to the ABR, there were no distinct differences in the wave V between adults and children. These findings are consistent with the appearance of the ABR having adult-like latency and amplitude values by 18 months to two years of age (Gorga et al., 1989; Hecox & Galambos, 1974; Salamy et al., 1975). Moreover, for both the adults and children, responses revealed a small asymmetry between the contralateral and ipsilateral group averages, with the peak of wave V on the contralateral side being slightly smaller. This observation is consistent with the findings reported by Hughes, Fino, and Gagnon (1981), who found the tendency of wave V amplitude to be smaller contralaterally, compared to the ipsilaterally recorded waveform.

In contrast, but also as expected, the MLR waves N_a and P_a elicited in children differed from adults in virtually all measurement parameters. In addition, the morphology of the N_a-P_a waveform in children was only of fair quality. Although the N_a-P_a waveform was identifiable, its peak was not a sharply delineated. One possible reason for this outcome is an interaction between the age of the children tested (i.e., younger than 10 years) and the stimulus rate used (i.e., slower rates may be needed for optimal wave definition in children). Otherwise, the only fair morphology of the MLR seems most likely a reflection of the immaturity of the generators of the middle latency components in children of the age test (and younger). Nevertheless, the data reported here concur with those published by Ruth and Tucker (1996), who found that amplitude increases and latency decreases with increasing age. Our data are also consistent with the results published by McPherson et al. (1989) who revealed that N_a morphology becomes consistent only after the age of eight, and, again, Ruth and Tucker who found that the P_a peak becomes better defined after the age of 12.

Likewise, the LLR waves P_1, N_1 and P_2 elicited in the pediatric subjects differed from the adults in virtually all measurement parameters. These results underscore that the overall morphology, amplitudes and latencies of these waves, indeed, reflect well on-going maturation. Namely, the current results are consistent with other studies, such as Cunningham et al. (2000), Kraus et al (1996), Ponton et al. (2000) and Wunderlich et al. (2006), who assert that the amplitude for N_1 and the peak of P_2 increases systematically with age. In addition, the latency of P_1 and N_1 decreases and P_2 increases with age. Moreover, in the current study an asymmetry was present between the contralateral and ipsilateral group averages. This disparity between sides of stimulation may be attributed to the fact that the contralateral pathway is the dominant route to the cortex. Although strength, location and direction of the dipole sources must be

considered it may not follow intuition (Butler, Keidel, & Spreng, 1969; Vaughan & Ritter, 1970; Jin, Ozaki, Suzuki, Baba, & Hashimoto, 2008). The asymmetry found in the present study was more pronounced in the grand averages of the LLR elicited in children than in adults. We speculate that this too reflects differences in pathway maturation between adults and children.

Test-retest comparisons demonstrated fairly good replicability, however, an examination of P_2 shows that the amplitude is higher and the latency is longer in the retest response. One possible reason for this outcome is that subjects were more attentive to the counting task during retest. Several investigators found that even with a less-demanding task of counting or attending to clicks produced larger amplitudes than those obtained during tasks that required the subject to read or perform perceptual discrimination (Gross, Begleiter, Tobin, & Kissin, 1965; Keating & Ruhm, 1971; Picton & Hillyard, 1974; Picton, Hillyard, Galambos, and Schiff, 1971; Satterfield, 1965).

6.1.2 Temporal Analysis of quasi-steady-state responses

The data reported here confirm, in effect, previous reports in which stimulus rates of 2/s or less are most appropriate to elicit the LLR (see Hall, 1992 for review; Nelson et al., 1997). At 0.75 Hz the P_1-N_1-P_2 complex was clearly evident, namely as a train of P_1-N_1-P_2 complexes across the capture window and despite the reduced temporal resolution (compare to the standard transient stimulus-response protocol. This observation was anticipated having implemented the same stimulus parameters between protocols. The data reported here also showed a clear P_1-N_1-P_2 complex at 1.25 Hz. However, when the modulation frequency was increased to 2.5 Hz, definition of the complex, per se, was greatly degraded. Although grand averages of the ASSR waveforms across all test groups were qualitatively similar, it thus was not clear that the

waveform literally represented the LLR. It was not expected that waveform responses would resemble any of the long latency components when the frequency was increased to 5 Hz and above, as was the case. By10 Hz and above, on the other hand, it was observed that the overall waveform captured reflected a mid-to-long-latency-like complex, that is, associated with the onset of the stimulus pulse train, which well persisted into the higher modulation frequencies. This was interpreted to be the effects of temporal integration over the repeated stimuli at such high rates and the windowing thereof. Specifically, the refresh cycle of the stimulus-response acquisition introduces (unavoidably) enough of a break to cause an on-effect of the acquisition window. At the same time, as the modulation frequency got closer to 40 Hz, the waveform microstructure progressively approached the continuous quasi-sinusoidal signals, as originally reported by Galambos et al. (1981). Thus, at 40 and 80 Hz, the recordings were typical of the conventionally recorded ASSRs at these modulation/repetition rates. In addition, as expected, there was good stability in the within- and between-test session reliability for these responses.

6.2 SPECTRAL ANALYSIS

6.2.1 Analysis of quasi-steady-state responses

Data reported here show harmonically related frequency components across all test groups at each modulation frequency. Several ASSR studies have shown the presence of harmonics at modulation frequencies, i.e. between two and 54.7 Hz (Picton et al., 1987), between five and 20 Hz (Rees et al., 1986), between 10 and 20 Hz (Pastor et al., 2002; Rob et al., 2000), between 30 and 190 Hz (Cohen et al., 1991), and between 40 and 200 Hz (Aoyagi et al., 1993). Stimulus

characteristics may have contributed to the difference in number of harmonics identified at corresponding modulation frequencies in the past studies, compared to the present study. Brief sinusoidal pulses (tone bursts) were used in the current study, whereas AM tones and clicks were used in previous ASSR studies. A relatively rich harmonic structure thus was anticipated and, indeed observed.

Although individual responses naturally demonstrated variability across subjects, they all demonstrated clear spectral peaks at harmonic frequencies that fell within the response characteristics of the grand average. Appendix D shows a subsample of 8 subject's data, half of which are more-or-less characteristic of the central tendencies represented by the grand average of the adult ASSR power spectra (cf. Figure 26) and half who demonstrated more-or-less extreme departures from the group average. In addition, the last panel shows the comparison of the N-of-25 reference spectrum and the grand average of spectra from the sub-sample of selected cases.

Less obvious was the spectral envelope that might be obtained, especially at the lowest modulation rate and the very low spectral power at the fundamental. This proves to be a nuance of a train of P_1-N_1-P_2 complexes and the low duty-cycle of this signal at 0.75 Hz, namely a relatively long interstimulus-interval (Figure 65). In addition, the spectral envelope is substantially dictated by the P_1-N_1-P_2 complex, which is revealed by comparing the spectrum of the simulated steady-state response and that of the single response (Figure 66).

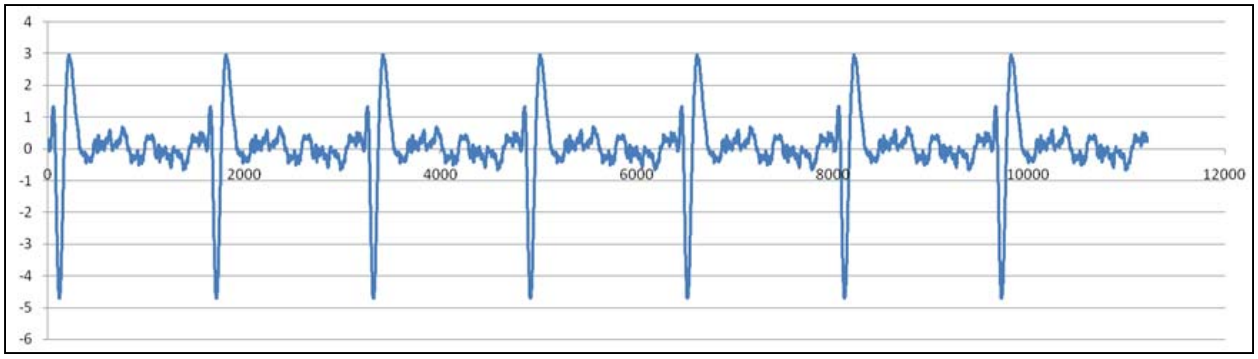


Figure 65 Capture window of quasi-steady-state model response

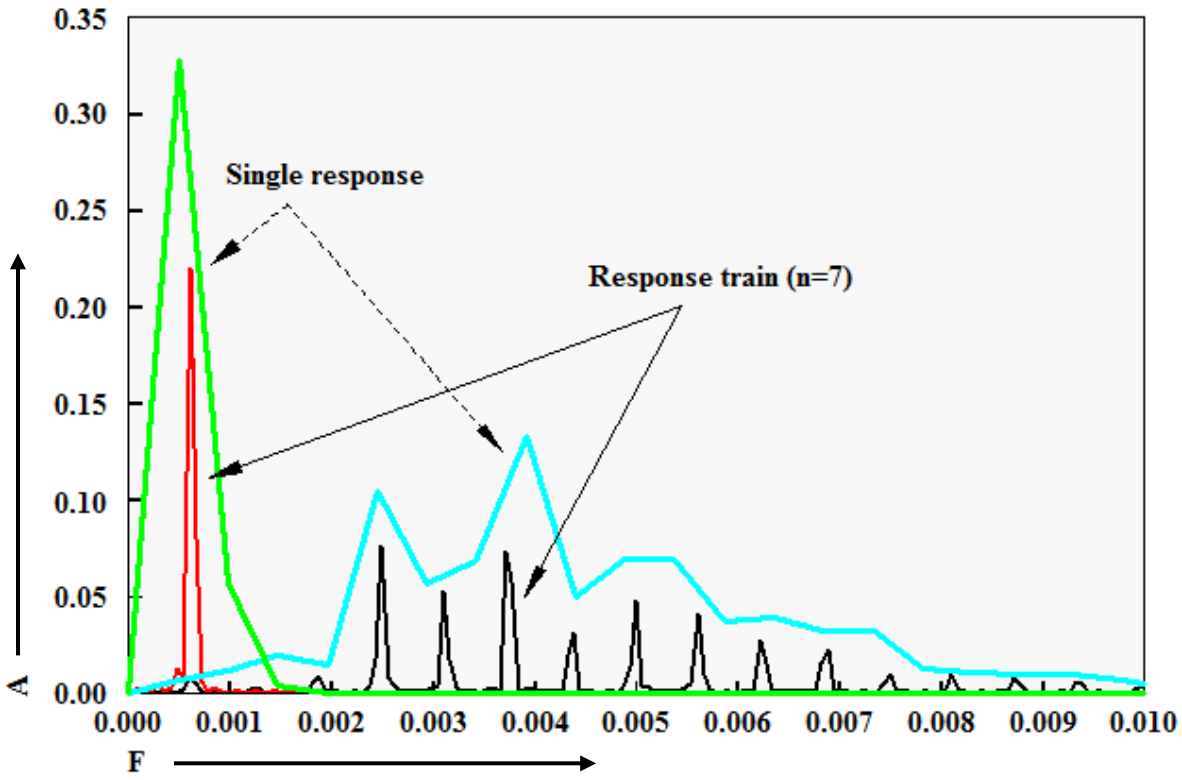


Figure 66 Spectrum of simulated steady-state response vs. single response

Furthermore, as expected, there was good stability in the within- and between-test session reliability for both adults and children. However, at 0.75 Hz the spectrum of the averaged responses of the retest shifted toward the lower harmonics. This shift repositioned the component that demonstrated the highest amplitude from the sixth harmonic (4.5 Hz) for the original test to the fundamental frequency in the retest. Basing the analysis only on the fundamental frequency would have biased the amplitude of the response in the retest. Thus, the effect would have been viewed as just an increase in amplitude at the fundamental frequency, a not too specific effect that might be taken to indicate that subjects were more attentive to the counting task in the retest, compared to the original test. However, since more information about the response at 0.75 Hz is revealed via spectral analysis, it is tempting to speculate that this shift in the spectral power toward the lower harmonics reflects some underlying process/activity that is not apparent or obvious when viewed via conventional temporal analysis. Alternatively, should the shift be due to a change of attention, this could prove to be a more specific marker than an overall change in amplitude which, in turn, may arise from a variety of factors.

6.2.1.1 Effects relative to 'adult awake' response

At low modulation frequencies in children (0.75-5 Hz) and in adults during sleep (0.75-1.25 Hz); the amplitude of the averaged response was significantly larger than those obtained in adults while awake. Since it is known that cortical responses reach maturity as late as adolescence, it is possible that the larger amplitude observed in the pediatric sample might be attributed to the mechanisms underlying the maturation of the cortical auditory structures, including the development of synaptic connections (Nelson et al, 1997). In addition, sleep outcomes in the present study are consistent with findings of Naka et al. (1999) who investigated the effects of sleep on auditory evoked magnetic fields. Naka and colleagues found that amplitudes of M150

and M200 (probably corresponding to N_1 and P_2 in the present study) were significantly enhanced during sleep stage 1 and 2, compared to the same components in the awake state. The authors proposed that the enhancement of the amplitude may be due to a decrease in the cognitive processing system at the cortical level.

However, unlike results at the lower modulation frequencies, the relative amplitude of the averaged response at 20 and 40 Hz in children and in adults during sleep was considerably smaller, compared to responses obtained in adults while awake. This result is consistent with results from other ASSR studies that have evaluated the effects of natural sleep and sedation on ASSRs (Cohen et al, 1991; Levi et al., 1993). In addition, this result is in accordant with other investigators that have suggested that transient evoked potentials with similar latencies (e.g., cortical and subcortical potentials) are affected by maturation (Ruth & Tucker, 1996; Wunderlich et al., 2006), and natural sleep (Jones & Baxter, 1988; Weitzman & Kremen, 1965; Williams et al., 1962). Furthermore, the relative amplitude of the response at 80 Hz was consistent across all test groups, which has been widely observed by others.

6.3 GROUP DATA ANALYSES

Findings of the present study reveals that the number of harmonically related frequency components identified in the ASSR power spectra across all test groups, decreased as modulation frequency increased from 0.75 to 80 Hz. Although, the effects of modulation frequency on ASSR amplitude are widely known, it is difficult to extract any meaningful comparisons to the present study due to the lack of uniformity in denomination of the amplitude measure of the response. The amplitudes reported in ASSR studies were based on several different measures

including peak-to-peak amplitudes (Kuwada et al., 1986; Stapells et al., 1984; Suzuki and Kobayashi, 1984), baseline-to-peak amplitudes (Lins et al., 1995), Batra's technique (Aoyagi et al., 1993; Batra et al., 1986), individual amplitudes, or vector averaging (Picton et al., 1987), the square root of the power of the FFT (Pastor et al., 2002), and amplitudes based on discrete Fourier coefficients (Rob et al., 2000). Of these studies, five reported the presence of harmonics (Aoyagi et al., 1993; Pastor et al., 2002; Rees et al., 1986; Rob et al., 2000), however, only two have reportedly included these components in their overall amplitude measure of the response (Pastor et al., 2002; Rob et al., 2000). Only two studies parallel the present study enough to allow a critical comparison.

Rob et al. investigated the effects of modulation frequency on ASSR amplitude using AM tones at 30 different frequencies, ranging from 10 to 100 Hz. Power spectra consisted of discrete lines at the fundamental frequency and subsequent harmonics. Using MEG, ASSR source amplitudes were smallest at 10, 30 and 100 Hz. Maximum responses were at 20 and 40 Hz. Similarly, Pastor et al. investigated the effects of modulation frequency on ASSR amplitude using clicks at 12 different modulation frequencies, ranging from 12 to 60 Hz. Stimulus rate lock responses to the fundamental frequency and upper harmonics were measured. Using functional brain imaging with positron emission tomography (PET), the amplitudes of steady-state scalp EEG responses were smallest at the lowest and highest modulation frequencies. Maximum responses occurred at 40 Hz. The present findings are similar to results of these two studies, in that the relative amplitudes were smallest at 10 and 80 Hz. Maximum responses occurred at 0.75 and 40 Hz.

However, basing group analyses only on the fundamental frequency would have biased the amplitudes across all test groups. Analyzing data in this way overestimates the amplitude of

the response at some modulation frequencies and underestimates it at others. Using the HS reveals the overall amplitude measure of the response, namely by incorporating more comprehensively the response information.

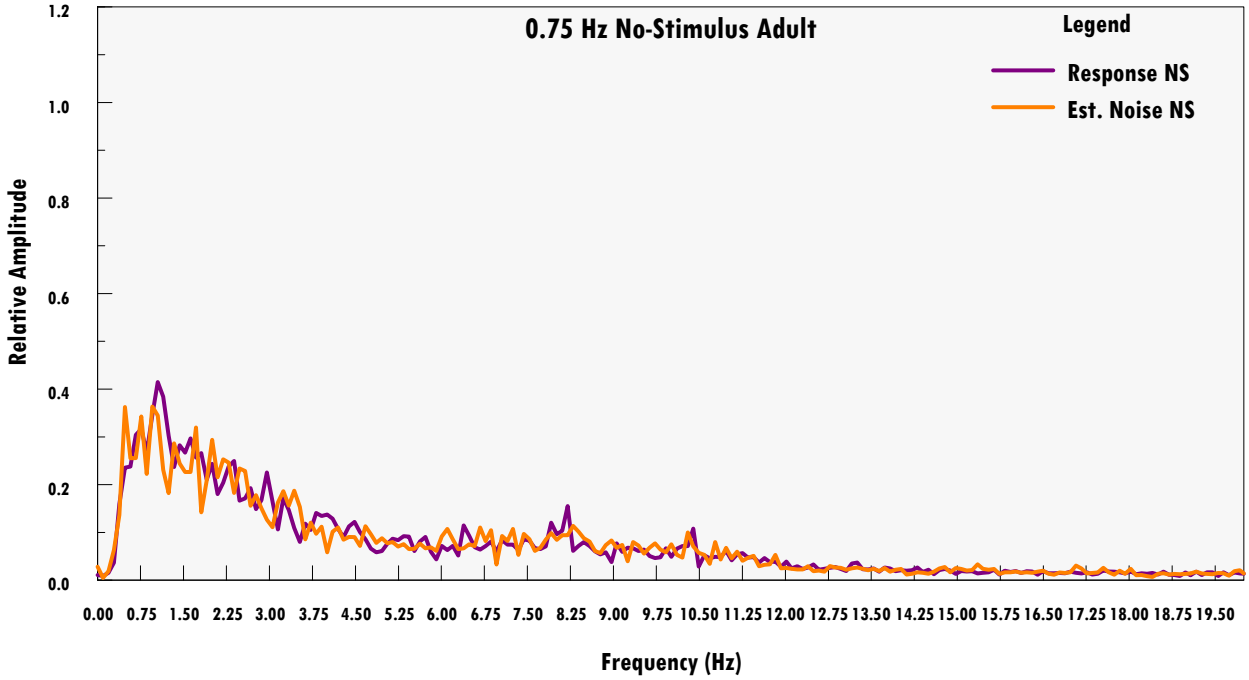
6.4 NO-STIMULUS CONDITION

In conventional transient response (temporal) analysis, it is possible to have chance appearances of waveforms that resemble a stimulus-evoked response. Because time and spectral analyses are fundamentally interchangeable, it seemed conceivable that aberrant spectral components might present under conditions for which there should be nothing because there is no stimulus. To this end, the response spectra and noise spectra for the adults and the children, and their corresponding no-stimulus control trials were superimposed in representative figures.

6.4.1 Adults

Figures 67 and 68 illustrate results from the no-stimulus conditions for adults. Visual inspection reveals that the no-stimulus spectra's at 0.75 and 10 Hz do not represent the harmonic structure that was identified in their corresponding stimulus-conditions. Nevertheless, there are some aberrant frequency products visible in the spectrum. At worst, these spurious signals can only account for a minor portion of the results. When the no-stimulus response was directly compared to the corresponding average adult response, the no-stimulus response falls about 30% or less of the scale relative to the average adult response for 0.75 Hz. Likewise, the no-stimulus response falls about 50% or less near the fundamental frequency, and thereafter falls about 20%

or less of the scale relative to the average adult response for 10 Hz. In addition, it appears that the no-stimulus response spectrum has nearly the same order of magnitude as the estimated no-stimulus background noise. When the no-stimulus noise spectrum was directly compared to the corresponding noise spectrum in the adult-awake sample, both show nearly the same order of magnitude at both 0.75 and 10 Hz.



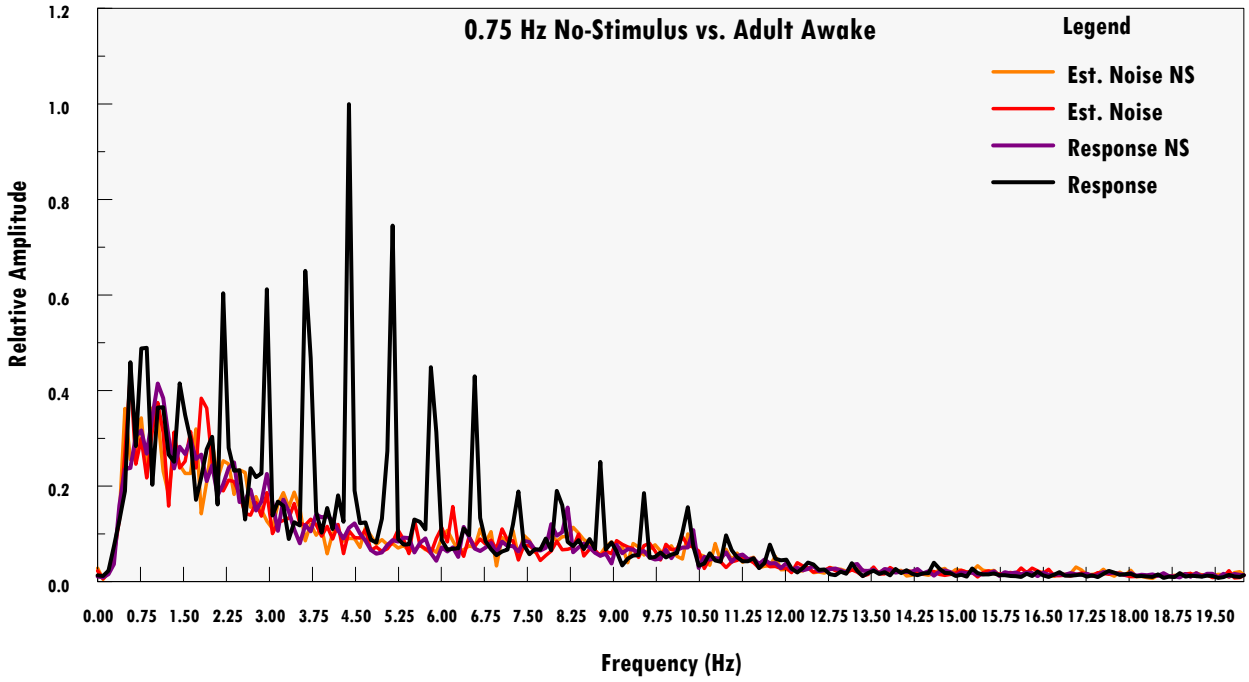
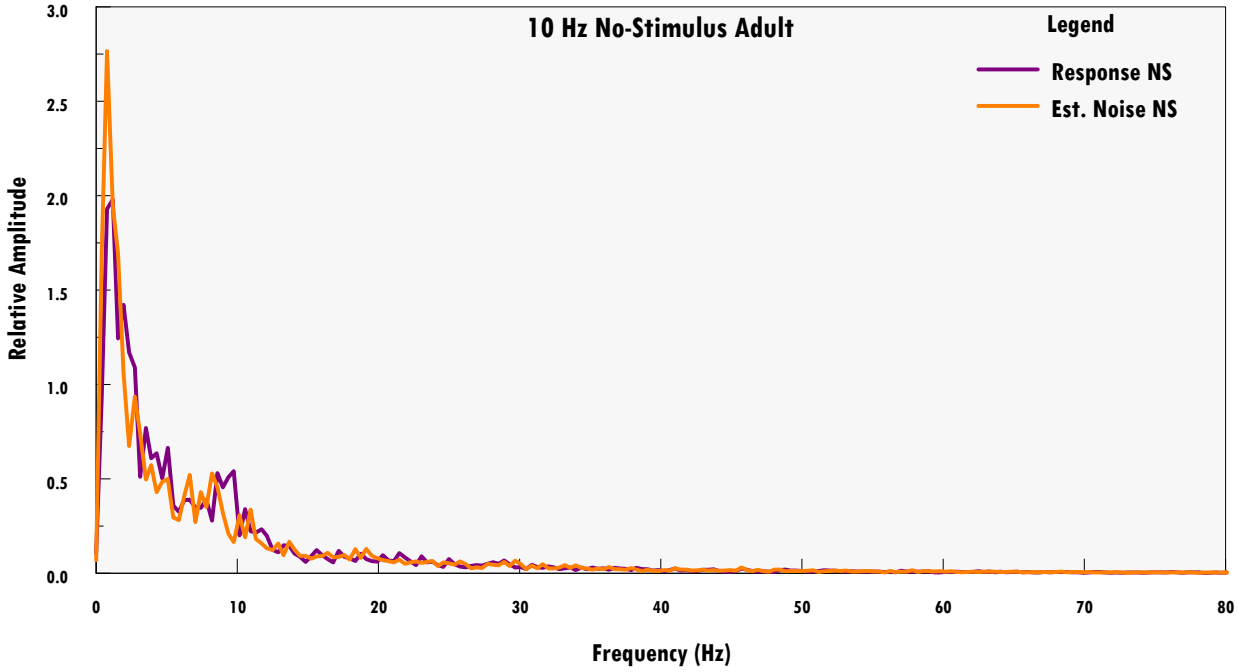


Figure 67 No-Stimulus at 0.75 Hz adults and comparison



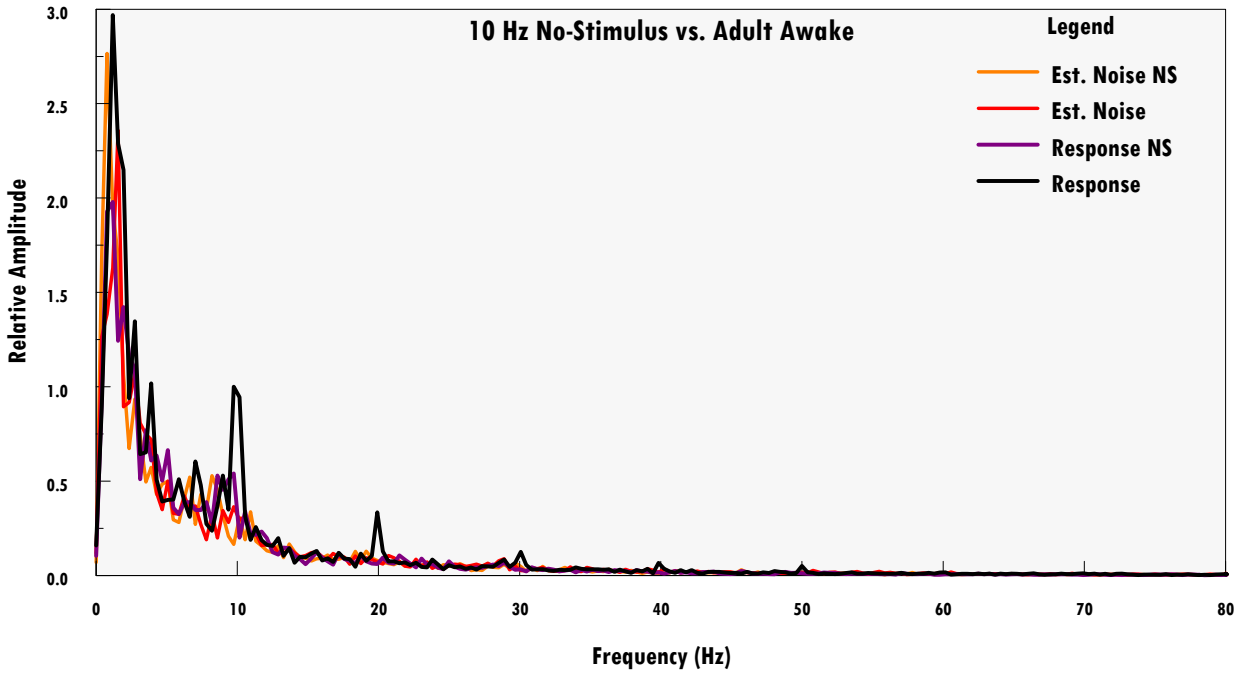
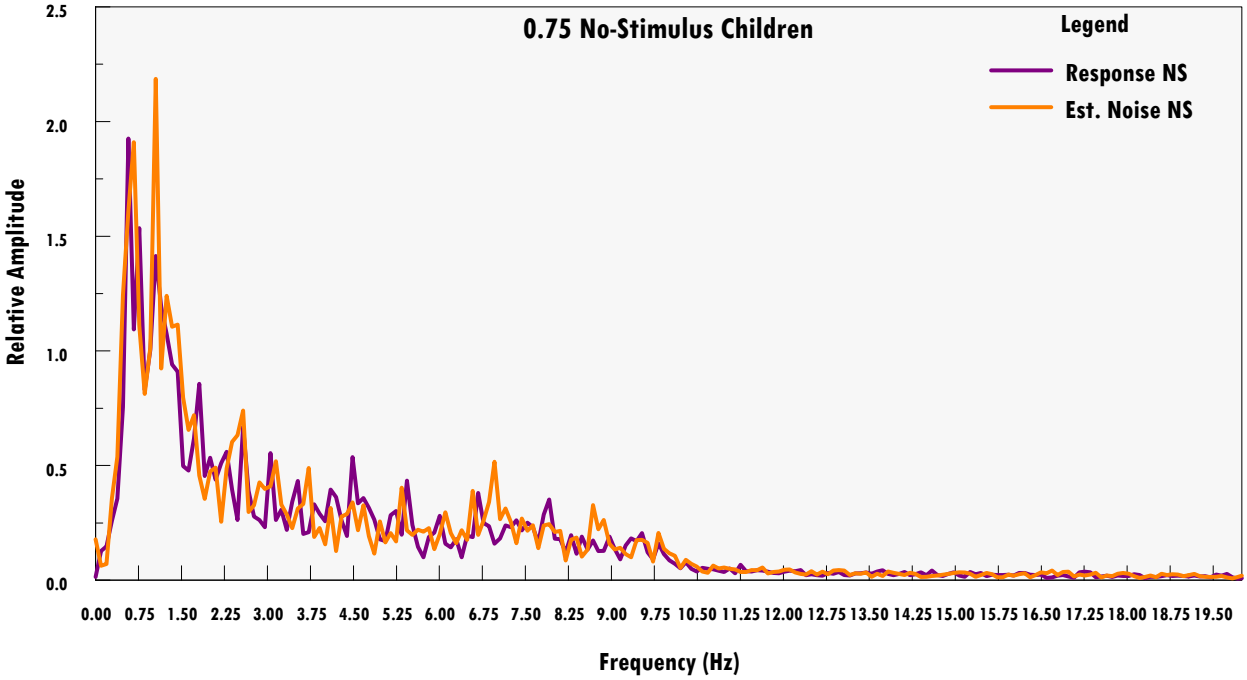


Figure 68 No-Stimulus at 0.75 Hz adults and comparison

6.4.2 Children

Figures 69 and 70 illustrate the no-stimulus conditions employed for children. Visual inspection reveals that the no-stimulus spectra's at 0.75 and 10 Hz do not represent the harmonic structure that was identified in their corresponding stimulus-conditions. Nevertheless there are some aberrant frequency products visible in the spectrum. At the worst, these spurious responses can only account for a minor element of the results. When the no-stimulus response was directly compared to the corresponding average child response, the no-stimulus response falls about 100% near the fundamental frequency, 40% at the second harmonic, and thereafter falls about 20% or less of the scale relative to the average child response for 0.75 Hz. Likewise the no-stimulus response falls about 50% near the fundamental frequency, and thereafter falls about 15% or less of the scale relative to the average child response for 10 Hz. In addition, it appears that the no-stimulus spectrum has nearly the same order of magnitude as the estimated no-stimulus background noise. When the no-stimulus noise spectrum was directly compared to the corresponding noise spectrum in the child sample, the former falls about 100% near the fundamental frequency and second harmonic, and thereafter falls about 20% or less below the latter at 0.75 Hz. Likewise, when the no-stimulus noise spectrum was directly compared to the corresponding noise spectrum in the child sample, the former falls about 25% or less of the scale relative to the noise spectrum in the child sample at 10 Hz.



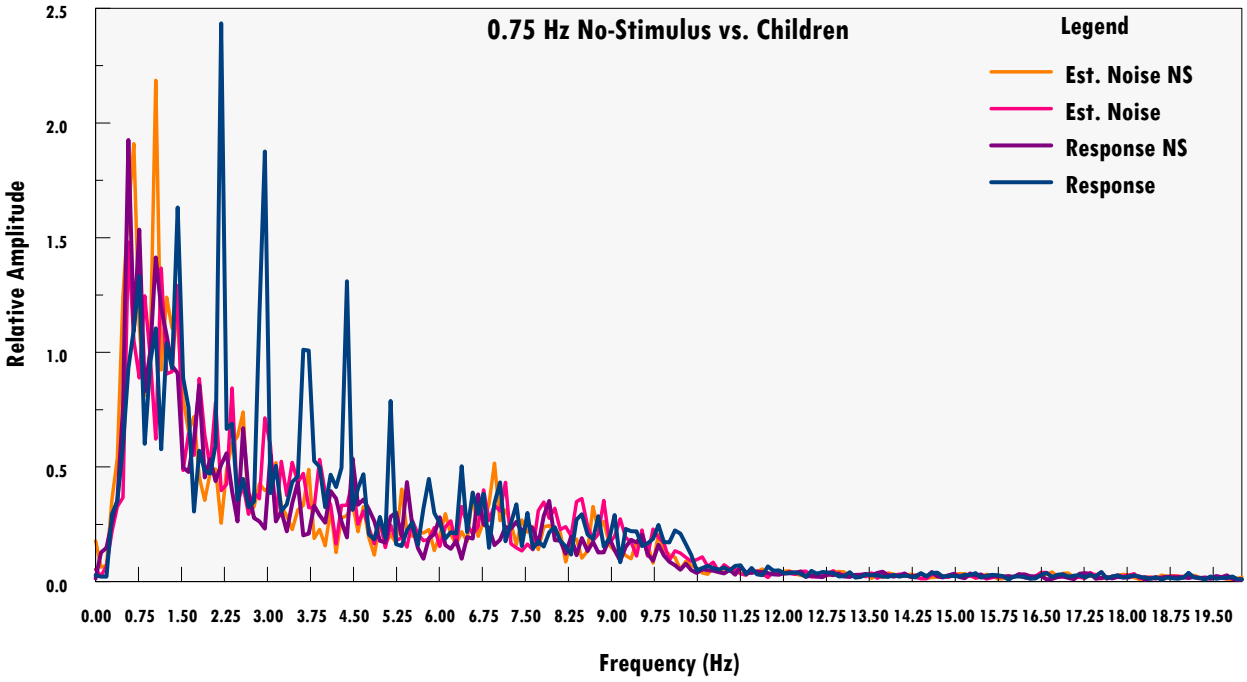


Figure 69 No-Stimulus at 0.75 Hz children and comparison

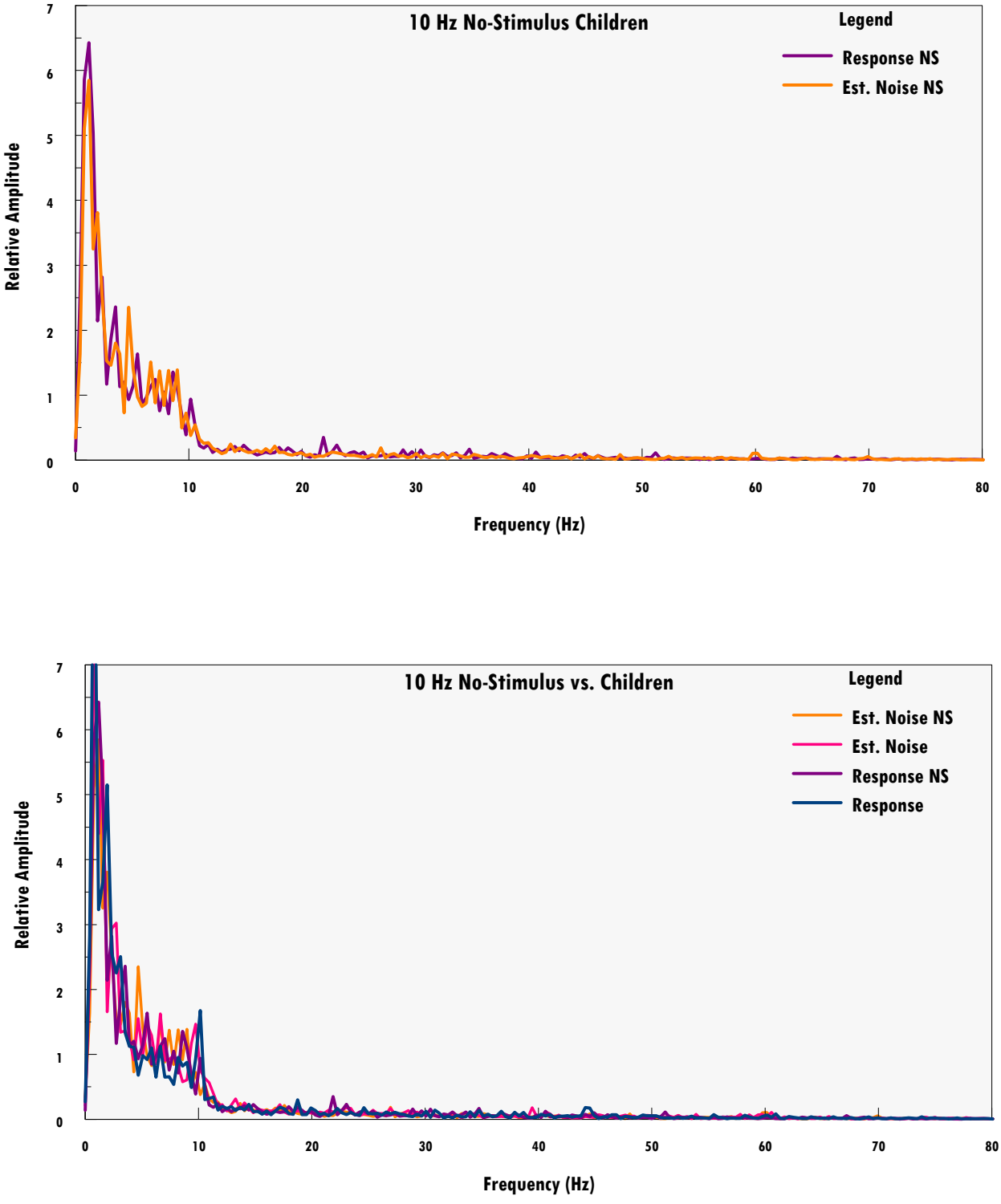


Figure 70 No-Stimulus at 10 Hz children and comparison

Therefore, there were no clearly salient harmonic products that were similar to those identified under the corresponding stimulus-conditions. In addition, the series of spectral components identified in the corresponding stimulus-conditions far exceeded the total estimated no-stimulus response and noise floor at 0.75 and 10 Hz for both adults and children.

7.0 CONCLUSIONS

This study profiled auditory steady-state response amplitudes in children and in adults over a wide range of repetition rates (modulation frequencies), specifically a range well embracing component waves of conventionally stimulated and recorded, transient, obligatory AEPs. Response amplitudes were measured at repetition rates from 0.75 to 80 Hz. Repetition rates of 10 Hz or less have received little attention in the context of the ASSR approach which is speculated to provide technical advantages, if not additional information, to the more traditional transient stimulus-response protocols, at least for some applications as follows: (1) to permit characterization of subject age-dependent amplitudes; (2) to allow an exploratory examination of the effects of repetition rate on response amplitude during natural sleep, to demonstrate if results differed from those obtained when subjects were awake, and (3) to further explore the use of both the fundamental and harmonics in the characterization of the response amplitude versus the typical measure of amplitude in transient stimulus-response analysis. Planned comparisons thus were conducted to evaluate the amplitude differences observed between the age groups (i.e., children and adults) and among the arousal groups (i.e., adults awake and adults asleep) on the repetition rates of 10 Hz or less. Responses also were evaluated above 10 Hz to permit comparisons across subjects and conditions and between results of the present and previous studies for this more established range of repetition rates, namely those embracing the auditory middle and short latency responses, the 40- and 80-Hz ASSRs, respectively.

Results of this study have shown that mean response amplitudes for children were significantly greater than those for adults at modulation frequencies of ≤ 5Hz. For adults and children, the relative amplitude was largest at the two lowest modulation frequencies. There was good reliability of the response measures across time points for testing both adults and children. In addition, mean response amplitudes for adults during sleep were significantly higher than those for adults while awake at the two lowest modulation frequencies. For adults during sleep, the relative amplitude was largest at 1.25 Hz. There was good stability of the responses between the two states of arousal in adults at 0.75, 1.25, 20, 40 and 80 Hz, whereas notably less consistent responses were observed at 5 to 20 Hz modulation. Furthermore, the results of this study have shown that the number of harmonically related frequency components identified in the ASSR power spectra across all test groups, decreased as modulation frequency increased from 0.75 to 80 Hz. Analysis based on the harmonic sum appears to improve the stability of response measures by incorporating response information carried by the upper harmonics, as well as the fundamental frequency, at least for low repetition rates where the harmonic spectrum is robust.

These findings potentially advance the clinical application of the ASSR approach. Responses obtained are expected to be comparably accessible in subjects at different stages of development and the brain-injured. Spectral measures themselves are rich and expected, at least, to substantially supplement more conventional methods as the contrasts of results across the conditions and groups tested in this study will translate as well into sensitivities to other developmental changes and/or brain damage. The outcomes of this study thus have established a foundation for future investigations regarding normal maturation, and the potential to explore injured-brain function and investigations regarding neurologic disorders across levels of central

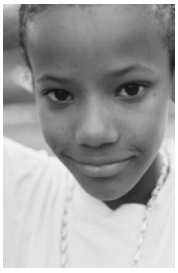
auditory system and warrant further research and development of the ASSR approach applied to a comprehensive range of modulation frequencies.

Appendix A

FLYER USED TO RECRUIT SUBJECTS

Research Study

Auditory Evoked Potentials: Profile in Children vs. Adults



The primary aim of this research study is to look at how auditory electrical responses change with age in children and adults. The secondary aim is to look at how these electrical responses *(in adults only)* change during sleep. We are seeking normal-hearing females 6 to 9 and 18 to 35 years of age, with no personal history of otological or neurological disorders.

An interview and an audiological screening will be conducted to determine eligibility for this study. For the primary aim of this study, those eligible will be asked to remain awake and alert during experimental testing. For the secondary aim of this study, adults will be asked to fall asleep while recording.

Participants receive a hearing assessment at no cost and remuneration will be provided.

If interested in discussing the possibility of having you or your child participate in this study please contact:
Abreena Tlumak
University of Pittsburgh
School of Rehabilitation Sciences
(412) 383-6576

Appendix B

VERBAL SCRIPT USED FOR RECRUITMENT

My name is Abreena Tlumak and I am a researcher at the University Of Pittsburgh School Of Rehabilitation Sciences. I am conducting a research study in which the primary aim of is to look at the how auditory electrical responses change with age in children and adults. The secondary aim is to look at how these electrical responses (in adults only) change during sleep.

I am seeking normal-hearing females 18 to 35 years of age, with no personal history of otological or neurological disorders.

An interview and an audiological screening will be conducted to determine eligibility for this study. For the primary aim of this study, those eligible will be asked to remain awake and alert during experimental testing. For the secondary aim of this study, adults will be asked to fall asleep while recording.

Participants receive a hearing assessment at no cost and remuneration will be provided.

If interested in discussing the possibility of participating in this study please write your name on the attached sheet along with a phone number that you can be reached, as well as an e-mail address that you most frequently use.

Thank you for your interest,
Abreena Tlumak

Appendix C

SCREENING SCRIPT USED TO DETERMINE ELIGIBILITY

Thank you for meeting with me/calling me to find out more about our research study. My name is Abreena Tlumak and I am a researcher at the University Of Pittsburgh School Of Rehabilitation Sciences. This research study is designed to look at how auditory electrical responses change with age in children and adults, and how these electrical responses *(in adults only)* change during sleep.

This study has both screening and experimental procedures. All methods employed in this study are procedures used in routine clinical and diagnostic testing with children and adults and pose no known risks.

Screening Procedures:
Screening procedures which will determine your/your child's eligibility include:
(1) A routine ear examination to ensure that you/your child's ears are not blocked by excessive wax, by a foreign object, or by the presence of any fluid.
(2) A routine clinical hearing test to ensure that you/your child's hearing is within normal limits.
(3) Testing to ensure that you/your child's hearing pathway appears healthy. This test is the auditory electrical response evaluation.

Experimental Procedures:
If you qualify to take part in this research study, you will undergo the following experimental procedures:
(1) Additional auditory electrical responses while awake (and for adults also during sleep).

The screening procedures will be obtained in the first session. The experimental procedures will be obtained in the second session (i.e., testing awake) and the third session if an adult (i.e., testing during sleep). Each session will last approximately 1.5 hours (not including breaks, which will be given as needed). All testing sessions will be held in the Physiological and Psychological Acoustic Laboratory, (Forbes Tower 5058). All sessions will be one to two weeks apart.

It is expected that only minor, if any discomfort will be experienced during auditory electrical testing. Occasionally, persons experience slight skin irritation from electrode preparation materials or paste, but the irritation subsides quickly after washing.

Other than receiving a hearing assessment at no cost, subjects are not likely to receive any direct benefit from participating in this study. However, if potential problems such as a hearing loss are noted, you will be informed of the concern and will be referred to appropriate professionals for additional testing and/or treatment. Remuneration will be provided for participants.

All records and identifying data (computer files, hardcopy files) will be locked in the investigator's laboratory. Only the investigator and people working with and for her will have access to identifiable data collected in the study.
Your participation in this study is voluntary and you may withdraw at any time.

Do you think you/your child might be interested in participating in this study?

No:

Thank you very much for calling/coming in.

Yes:

Before I enroll you/your child in this study, I need to ask you some questions relating to your/your child's hearing and balance. The purpose of these questions is only to determine whether you/your child are eligible for this study. Do I have your permission to ask these questions?

1. What is your/your child's age? _____ exclude if <6, 10-17, or >35)

2. Have you/your child had any ear infections that required ear surgery? Y (exclude) N

3. Do you/your child have a history of hearing difficulties? Y (exclude) N

4. Do you/your child experience dizziness or unsteadiness? Y (exclude*) N

* If associated with hearing loss

5. Do you/your child have any noise in either ear (e.g., ringing, buzzing)? Y (exclude*) N

* If unilateral

6. Have you/your child ever been placed on a drug regimen where you were warned of a possible change in hearing ability, which you/your child did in fact experience? Y (exclude) N

7. Have you/your child ever had a head injury which needed medical attention or been diagnosed with a concussion? Y (exclude) N

8. Have you/your child been diagnosed with a neurological disorder or been treated for a neurological disorder of the head or neck? Y (exclude) N

Thank you for taking the time to respond to these questions. Based on your responses, it looks like you are / are not eligible to participate in this study.

ELIGIBLE:

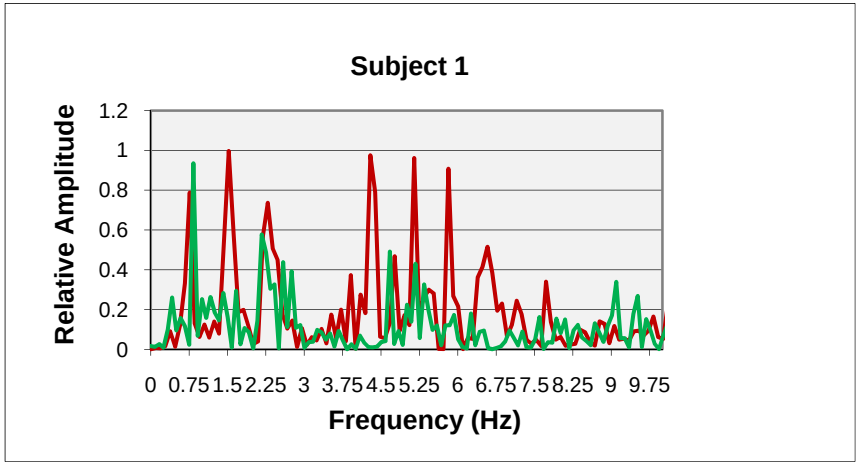
Children: The study will take approximately three hours to complete over two sessions. Would you like to set up a time to come in?

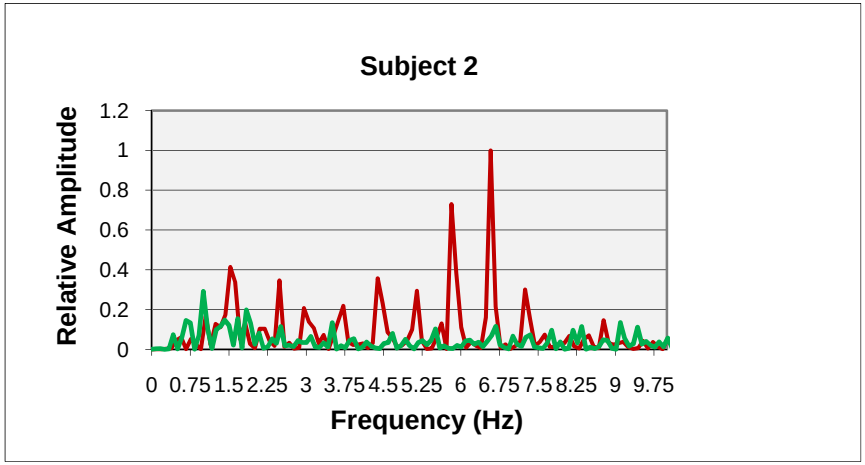
Adults in CSD Department participating in both the awake and sleep portions: The study will take approximately four and a half hours to complete over 3 sessions. Would you like to set up a time to come in?

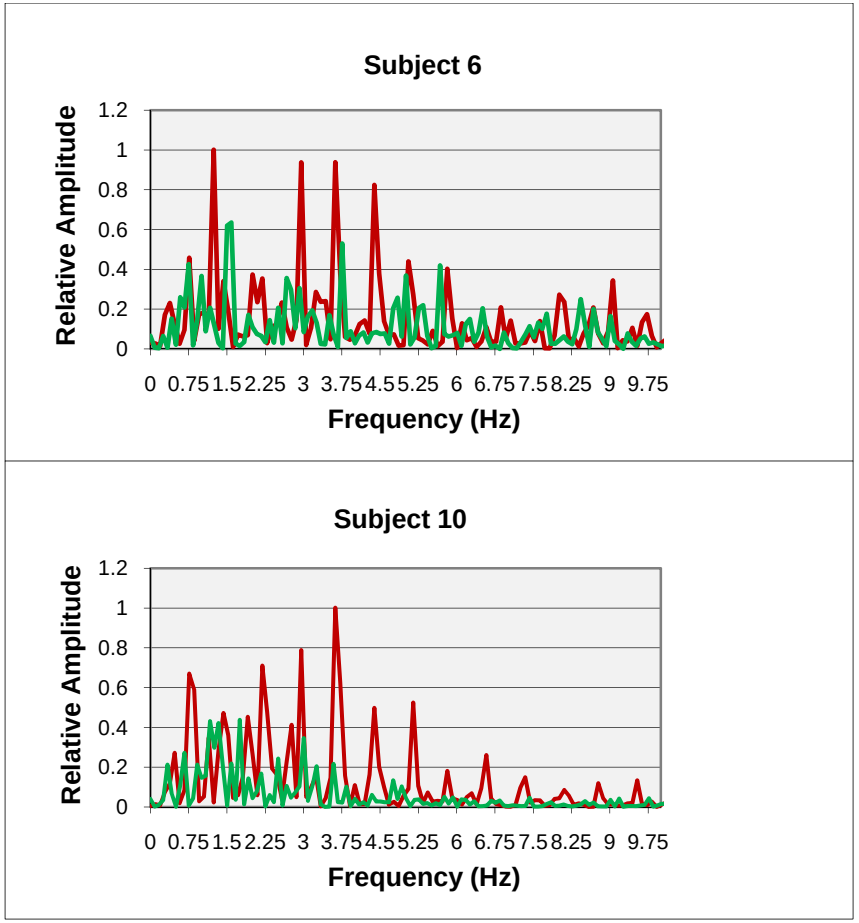
NOT ELIGIBLE: I'm afraid you're not eligible to participate in this study because of your responses to one or more of the screening questions. But thank you for your interest and good luck to you.

Appendix D

VARIABILITY OF INDIVIDUAL RESPONSES AT 0.75 HZ



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0.6
0.4
0.2
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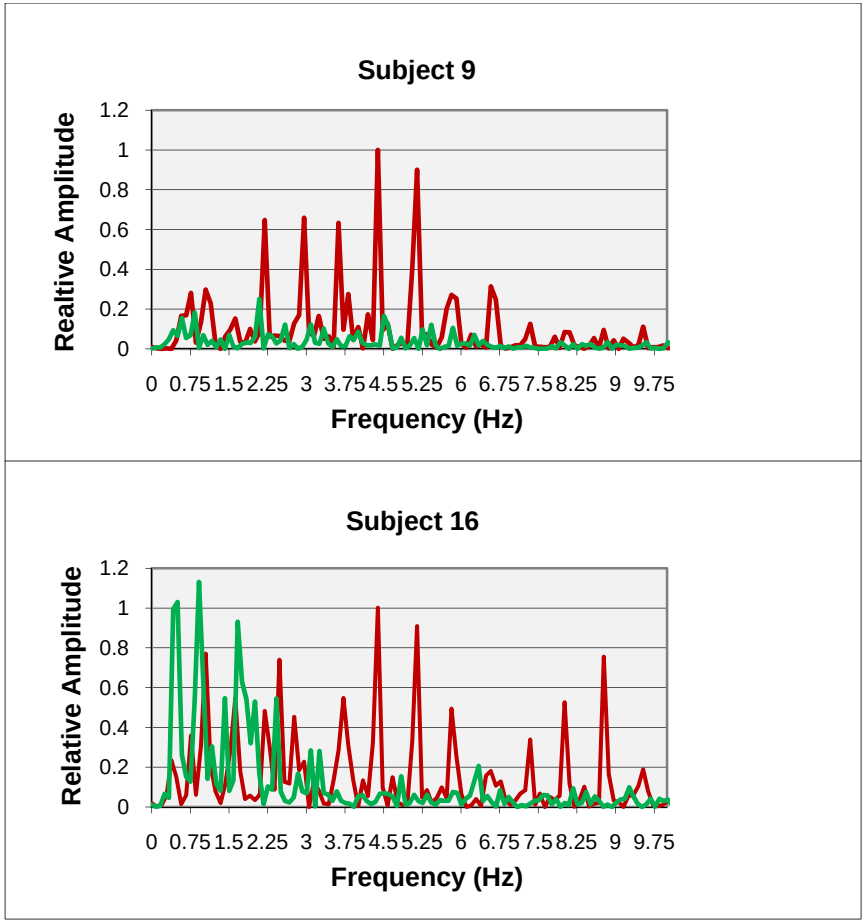
Frequency (Hz)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0.6
0.4
0.2
0
0 0.75 1.5 2.25 3 3.75 4.5 5.25 6 6.75 7.5 8.25 9 9.75
Frequency (Hz)

Subject 10
Relative Amplitude
1.2
1
0.8
0.6
0.4
0.2
0
0 0.75 1.5 2.25 3 3.75 4.5 5.25 6 6.75 7.5 8.25 9 9.75
Frequency (Hz)

Subject 16
Relative Amplitude
1.2
1
0.8
0.6
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0.2
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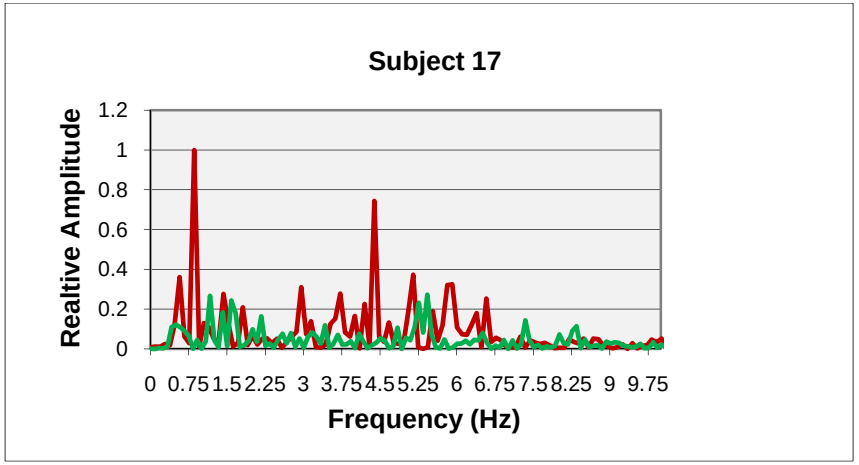
Frequency (Hz)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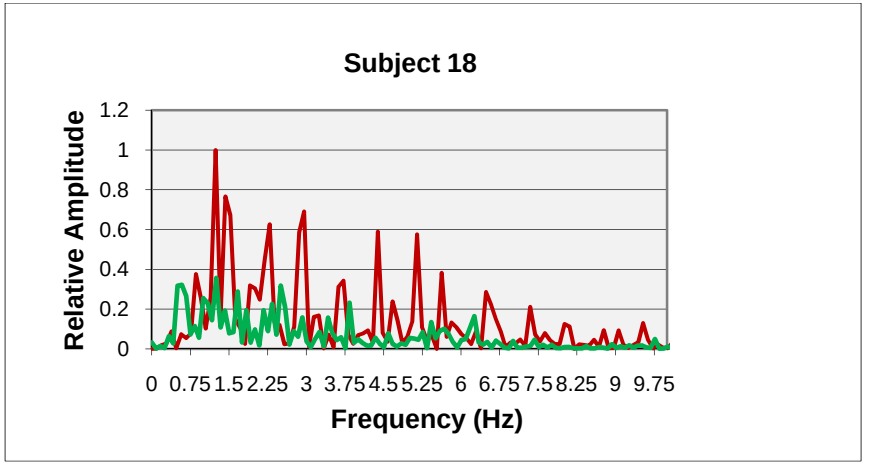
Frequency (Hz)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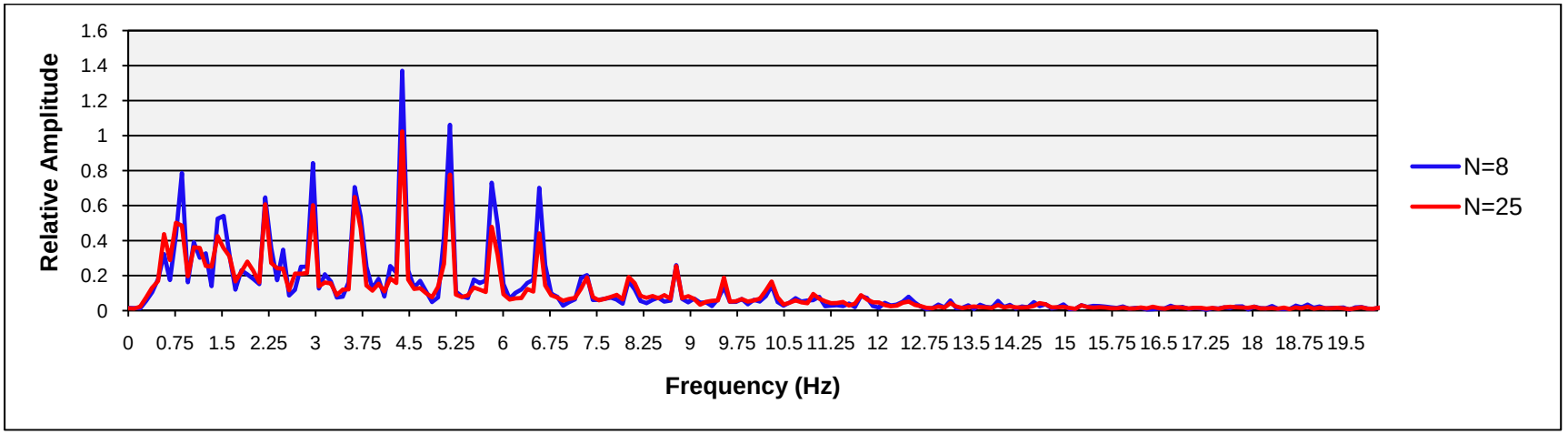
Frequency (Hz)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1.4
1.2
1
0.8
0.6
0.4
0.2
0
0 0.75 1.5 2.25 3 3.75 4.5 5.25 6 6.75 7.5 8.25 9 9.75 10.5 11.25 12 12.75 13.5 14.25 15 15.75 16.5 17.25 18 18.75 19.5
Frequency (Hz)
N=8
N=25

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