AUDITORY PROCESSING OF COMPLEX TONES IN NEWBORN INFANTS

by

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Abstract

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Pitch extraction from complex acoustic stimuli during neonatal period in infants was examined in this study. It is one of the most fundamental auditory processes. Pitch processing is crucial for speech intonation and musical melody perception. Preferences of newborns for "motherese" (or infant directed speech), which has different pitch characteristics compared to adult directed speech, suggest an early pitch information processing capability in newborns. Although auditory functional development in the auditory system at early ages draws much attention of researchers from different disciplines, the number of studies during the neonatal period is limited. We first asked how pitch information processing develops. It was hypothesized that newborns already possess ability to process pitch information early during perinatal period. Second, we hypothesized that the extraction of pitch information in acoustic stimuli depended on the integrity of the auditory pathway. Brain insult in the perinatal period has been shown highly likely to affect subcortical structures, including the auditory brainstem and midbrain, through different mechanisms. We reasoned that if there were delays in or problems with pitch processing in brain-injured or premature neonates when compared to healthy or premature infants of equal gestation, then, in the absence of peripheral disturbances, evidence for CNS mediation of the development of pitch processing could be argued.

Two types of auditory brainstem responses were studied: (1) auditory brainstem evoked responses (ABRs) to click stimuli, and (2) the frequency following response (FFR) to complex tones were utilized to study the above questions in N=128 premature and term infants assigned to the Neonatal Intensive Care Unit (NICU) at birth, all at varying risk for a CNS injury (mean gestational age at birth=34±3.6 weeks).

In summary, we confirmed that auditory pitch information processing of complex sound was present in newborn infants as early as 32 weeks gestation. Neonatal FFR studies provided positive evidence of responses to the pitch-related information both in the envelope-related frequency as well as in the difference tone and stimulus component-related frequencies. Similar responses at younger and older ages at test indicated that this capability remains stable across age during the first month of life. Moreover, NICU infants with evidence of a structural perinatal brain injury showed impairment in this type of auditory processing.

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Abbreviations

ABR	Auditory brainstem evoked responses
BI	Brain insult
BM	Basilar membrane
CFs	Component frequencies
CLs	Component latencies
CT	Computed (axial) tomography
CUS	Cranial ultrasound
CNS	Central nervous system
dB	Decibel
DP	Distortion product
DPOAE	Distortion product otoacoustic emission
EEG	Electroencephalography
ER frequency	Envelope-related frequency
FFR	Frequency following response
FFT	Fast-Fourrier transformation
GA	Gestational age
GLM	General Linear Model
GM	Germinal matrix
Hz	Hertz
ID speech	Infant directed speech
IHC	Inner hair cell

IPLs	Interpeak latencies
IVH	Intraventricular hemorrhage
LBW	Low birth weight
MMN	Mismatch negativity
MF	Missing fundamental
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
OAE	Otoacoustic emission
OHC	Outer hair cell
PCA	Postconceptional age
PVL	Periventricular leukomalacia
RUMC	Richmond University Medical Center, Staten Island
SVCMC	St. Vincent's Catholic Medical Center, Staten Island
VLBW	Very low birth weight

CHAPTER 1- INTRODUCTION

I. The auditory system and its function development

The human auditory system has been shown to have an early onset of function. Anatomically, auditory nerve fibers begin to myelinate as early as the third trimester. By term age, mature neurons are present in the superficial layer of the auditory cortex (Moore, 2002). Given the evidence of prenatal auditory behavior as well as electrophysiological evidence obtained in fetuses in utero and premature infants (Lecanuet, Granier-Deferre & Busnel,1988, 2000; Birnholz & Benacerraf,1983; Kisilevsky, Muir & Low,1992) it is reasonable to assume that full-term newborns emerge from the womb with at least some basic mechanisms to organize their auditory world. On the other hand, given the complexity of the auditory system as outlined in the following overview, it is harder to assume that neonates might have full adult capabilities for auditory function. This thesis was designed to address this issue by study early characteristics of pitch processing, a complex auditory processing capacity known present in adult capabilities, but not known as to its developmental origins.

A. Overview of the structure and function of the auditory system

The auditory system is often arbitrarily divided into peripheral and central auditory portions. The peripheral auditory system includes the structures from the external ear through the auditory nerve. The central auditory system begins at the cochlear nucleus and extends to the auditory cortex.

1. Peripheral auditory system

The peripheral auditory system is divided into the external, middle, and inner ear. The external and middle ear play a role in sound capture and mechanical amplification of sound

pressure. The inner ear is composed of the cochlea which subserves auditory function, and the vestibular system which assists in maintaining balance and posture.

The cochlea is "the most important part of the ear" and "an understanding of what goes on in the cochlea can provide a key to many aspects of auditory perception" (Moore, 1997). One of the major components of the cochlea is the organ of Corti first discovered by Corti in 1851. Embedded in the organ of Corti are the auditory sensory neurons or hair cells. The hair cells are divided into two groups, inner and outer hair cells. In humans, there are about 3500 inner hair cells (IHCs), each with about 40 apical projections (stereocilia) and 12000 outer hair cells (OHCs), each with about 140 stereocilia (Wright et al., 1987). Deflection of stereocilia causes the opening of transduction channels at the tip links. This results in the generation of hair cell transduction potentials that result in neurotransmitter release at presynaptic terminal with a nerve fiber, and generation of an action potential in the auditory nerve. Thus, the IHCs relay information from the cochlea to higher levels of the auditory system by causing release of neurotransmitters, which in turn evoke electrical signals in the auditory type I afferent fibers. OHCs are thought to play an important role in cochlear amplification via electromechanical feedback. OHCs also have been shown to have a motor function, by affecting the protein *prestin*, changing their length and shape in response to voltage difference across the membrane (see Fettiplace & Hackney (2006), for a review of auditory hair cells).

The basilar membrane (BM) in the cochlea plays a role in frequency selectivity and sharp tuning. It acts as a mechanical analyzer of sound frequencies, in which frequency sensitivity varies from the base to the apex. The base is relatively thick and taut. This results in high-frequency sounds (as high as 20 kHz in humans) producing a maximum displacement of the membrane. Low frequency sound (as low as 20 Hz in humans) produces vibration all along the

BM, but reaches a maximum at the thinner and floppier apex. Each point on the BM is sensitive to a certain frequency (characteristic frequency). This arrangement is an exemplar of a tonotopic map classically described by von Bekesy, 1960, and more recently reviewed in Moore, 1997. Response of the BM to sounds is non-linear. When a stimulus reaches its corresponding characteristic frequency on the BM, the magnitude of BM displacement can be amplified up to 60dB (Johnstone et al., 1986; Ruggero and Rich, 1991 in Hartmann 1998). This accounts for the sharp tuning characteristic of the BM.

BM nonlinearity also is reflected in the phenomenon of intermodulation distortion, which has been thought to play a fundamental role in the perception of sounds in humans. When simultaneously introducing more than one tone, additional tones (i.e., distortion products), which are not present in the acoustic stimuli, are generated. For two tones with different primary frequencies of f1 and f2, where f2 > f1, distortion products can be generated correspond to different combinations of the primary frequencies (e.g., 2f1-f2, 3f1-2f2, 2f2-f1, 3f2-2f1). Two-tone suppression, another property of BM nonlinearity, is the reduction of the response to one tone by the presence of another tone (reviewed in Robles & Ruggero, 2001).

Innervation of IHCs and OHCs is accomplished through different types and numbers of fibers within the auditory nerve. The fundamental characteristics of the auditory nerve fibers sub-serving IHCs are frequency selectivity and phase locking. The frequency selectivity of a single nerve fiber is often illustrated by a tuning curve, which shows the fiber's threshold as a function of frequency. Phase locking refers to the observation that neural firings tend to occur at a particular phase of the stimulating waveform, so that there is a temporal regularity in the firing pattern of neurons in response to periodic stimuli (reviewed in Moore, 1997).

Central auditory system

The first-order afferent or ascending auditory fibers terminate at the ventral and dorsal cochlear nuclei located within the lower brainstem (medulla oblongata). The ventral part of the cochlear nucleus sends second-order fibers to both the ipsilateral and the contralateral superior olive complex. There are also second-order fibers that cross over directly from one cochlear nucleus to the other. This connection, in addition to the inter-aural processing in the superior olive complex, facilitates the cross-ear temporal comparisons that play an important role in localization of sound sources. The dorsal cochlear nucleus sends second-order fibers to the contralateral lateral lemniscus and inferior colliculus. Some third-order neurons also reach the inferior colliculus after making synapses with the second-order neurons in the dorsal nucleus of the lateral lemniscus. In addition, the inferior colliculus receives fibers from the contralateral accessory superior olive and both the ipsilateral superior and accessory olive nuclei (reviewed in Moore, 1987).

The inferior colliculus is a major midbrain structure concerned with hearing (reviewed in Moore, 1987). In the mature brain, it receives ascending fibers from various ipsilateral and contralateral sites in the auditory brainstem and descending fibers from the cortex (Oliver et al, 1991). As a result of this extensive connection and because it is the primary source of projections to the thalamus and cortex, it is often considered to perform an "integrative" role in auditory processing. From the colliculus, fibers connect forward to the medial geniculate and also link to the reticular formation. There are no connections between the two medial geniculates, so that all subcortical lateral interactions occur below this level. In humans, there are approximately one million subcortical neurons on each side associated with the auditory pathway to the cortex. The cochlear nucleus has about 90,000 neurons, the superior olivary complex (together with the

trapezoid body) 34,000, the lateral lemniscus 38,000, the inferior colliculus 400,000, the medial geniculate 500,000 (Worden, 1971). This large number of neurons within subcortical regions relative to much smaller number of auditory nerve fibers (about 30,000) indicates the importance and complexity of subcortical processing.

Neurophysiological studies in animals showed that tonotopic organization of characteristic frequencies on the BM is preserved at different levels of the ascending auditory pathway. This frequency map is found in all three subdivisions of the cochlear nucleus (Rose, et al. 1959), superior olive complex (Goldberg & Brown, 1968), dorsal and ventral lateral lemniscus (Aitkin et al., 1970), inferior colliculus (Rose et al, 1963) (see Worden, 1971), ventral subdivision of the medial geniculate body (Aikins & Webster, 1971) and in the auditory primary cortex (Merzenich et al., 1975).

Anatomically, it has been shown that human subcortical structures mature early as indicated by the degree of myelination. Thisd was shown to occur in the human auditory nerve as early as the 20th week of gestation using light and electron microscopy (Ray et al., 2005). Cochlear nucleus, superior olive, lateral lemniscus and inferior colliculus are myelinated by the 29th week of gestation as indicated by histological studies (Moore, 1995), although MRI studies might indicate this does not occur until 2-3 weeks before term (37-38th gestational week; Sano et al., 2007). Using MRI, myelination was observed in the medial geniculate body as early as 28th week gestation Counsell, 2002), and in the reticular formation and corpus callosum at about 2-4 months after birth (Flechsig, 1920; Nakagawa et al., 1998; Sano et al., 2007).

In the cerebral cortex, the auditory cortex is located in the Sylvian fissure within the temporal lobes. Using neurofilament immunostaining as a marker of onset function, Moore (2002) has shown that from about 28th weeks gestation to 4 months after birth, the human cortex

has mature axons only in the superficial or marginal layer. This layer consists of projections that run parallel to the cortical surface and make contact to apical dendrites of deeper layer neurons. Through these apical dendrites, marginal layer axons drive the activity of the deeper cells and are believed to promote their structure and functional maturation. Yet, "these marginal layer axons constitute an intracortical system that carries little or no information on external auditory stimuli" (Moore, 2002). On the other hand, auditory cortical responses were recorded in fetus between 29 to 40 weeks gestational age using magnetoencephalography (i.e., Blum et al. 1985; Wakai et al., 1996., Zappasodi et al., 2001; Schleussner et al., 2001; Lengle et al., 2001; Eswaran et al., 2002)

In summary, given the complexity and extensive networks of the auditory system, its functional integrity from cochlear hair cells to higher-level centers is assumed to be required for normal auditory function development. On the other hand, auditory functional capabilities during development are assumed to reflect the underlying maturational stages of this auditory system development, but how this occurs or what specific functions are subsumed at any point is not necessarily know.

A. Auditory functional development

The evidence suggests that the human auditory system undergoes dramatic improvement in sensitivity between the onset of function in the last trimester of gestation and the end of the first postnatal year. Coinciding with anatomical evidence reviewed in the previous section, behavioral and physiological observations from the intact fetus and from infants born prematurely suggest that auditory function starts as early as 26-28th week of gestation. Auditory stimuli can elicit changes in heart rate (Lecanuet, Granier-Deferre & Busnel, 1988), eye blink (Birnholz & Benacerraf,1983), gross motor responses (Kisilevsky, Muir & Low,1992), and

APRs (Hall,1992). Early auditory functional capabilities allow infants to process acoustic signals and to be responsive to their surrounding environment. Preferences for certain classes of auditory stimulation and the ability to orient towards sounds is observed in newborns at birth. Other fundamental auditory capabilities, such as cochlear maturation, frequency and temporal resolution, absolute thresholds and intensity discrimination, have also been extensively studied during the first few postnatal months. Moreover, there is a large amount of research focused on infants' perception of complex auditory stimuli, including maternal speech, pitch perception of tonal complexes with a missing fundamental, music and tonal sequences. However, neonatal data are limited. A review of relevant literature on early infant auditory sensory and perceptual capabilities is provided below.

1. Fundamental auditory capabilities

a. Absolute threshold and intensity discrimination

Absolute threshold is the minimum detectable level of a sound in the absence of any other external sounds (Moore, 1997). The ABR is one of the methods to assess sound threshold in infants. Hecox (1975) found ABR in newborns is 10-15 dB less sensitive than in adults. When using observer-based observations of behavior, thresholds in newborns were estimated as approximately 35 dB poorer than adults at higher frequencies (above 2000 Hz) (Werner and Gillenwater, 1990; Tharpe & Ashmead, 2001). Hecox (1975) and Olsho et al (1988) documented significant improvements in absolute thresholds between 6 months and 2 years of age. The insensitivity of the auditory function in infants is thought to result partly from a higher level of internal noise, but also could depend on the techniques used to determine thresholds. Absolute thresholds in noise have not been obtained from newborns, but in 6- to 12-month-old infants the thresholds in noise are closer to adult values than those in a quiet testing environment (Nozza &

Wilson, 1984). This hypothesis of higher levels of internal noise in infants is supported by evidence from studies where auditory response depended on its effects on visually dependent responses. Estimating internal noise by adding external noise to a visual stimulus, Skoczenski & Aslin (1995) found that the level of external noise at which performance began to decline was much higher in infants than in adults.

Another factor that may play a role in limitation of infant auditory sensitivity is attention/motivation. This was suggested by the observation that intensity thresholds in 1-month-old infants were superior when a reinforcer was used to improve accuracy (Werner & Mancl, 1993). It also has been shown that intensity discrimination, examined by threshold to detect an intensity increment, improves from 6dB at 6 months of age to 4 dB at 12 months of age (Sinnot & Aslin, 1985; Schneider, Bull & Trehub, 1988).

b. Frequency resolution and auditory bandwidth

Frequency resolution refers to the ability to detect changes in stimulus frequency. A related measure is auditory bandwidth, referring to an ability to detect sounds at one frequency in the presence of sounds at other frequencies.

Frequency resolution can be measured using a pulsation threshold-masking paradigm. Pulsation threshold is the masker tone's intensity in which a pulsing tone is indistinguishable from a continuous tone. When examining the effect of masker frequencies on pulsation threshold, Spetner and Olsho (1990) showed that 6-month-olds' frequency resolution were similar to that of adults. Frequency resolution of 3- month-olds were adult-like at low frequencies (500 and 1000 Hz) but not at higher frequencies (4000 Hz) indicating that young infants are less able to resolve small differences in higher frequencies in the presence of other auditory stimuli.

Consistent with this finding, Abdala (1995) found the same development pattern of low versus high frequency resolution in 3-month, 6-month-old infants and adults while using tone-pip-evoked ABR recorded with notched-noise masking. It was suggested that immaturity of auditory brainstem and middle ear to high frequencies underlying this immature frequency resolution (Werner, 2007). Interestingly, Werner & Bagones (1991) showed that 6-month-old infants, although having adult-like frequency resolution, have higher thresholds when their attention is diverted from the task by distractors. Thus, attentional (distractor) task effects as opposed to an immature system can account for infants' poorer frequency resolution performance.

c. Temporal resolution

Temporal resolution refers to the auditory system's ability to follow rapid changes in the timing features of sound. Gap detection thresholds, which measure the ability to detect a brief interruption (gap) in a continuous broadband noise, are commonly used to examine temporal resolution. It can provide an estimate of temporal resolution based on a single threshold. On the other hand, this estimate also relies on intensity resolution (Werner, 2001). It was found that found that temporal acuity, by means of gap detection threshold, were not adult-like in 3-, 6- and 12-month-old infants (Werner et al., 1992). Also, using different stimuli, in this case short Gaussian-modulated sine-wave tones, the former observation of higher gap detection thresholds in infants compared to adults was replicated (Trehub, Schneider & Henderson, 1995).

To differentiate the peripheral and central sources of infants' poor temporal resolution, gap detection thresholds using ABR and psychophysical method were compared in 3-, 6-month-old infants and adults (Werner et al., 2001). Although in 3-month-olds psychophysical gap thresholds were much higher than those of adults, ABR gap thresholds were adult-like

suggesting that immaturity at the brainstem level is unlikely to account for infants' poor gap detection performance behaviorally.

Recently, the use of the mismatch negativity (MMN) component of auditory event-related potentials has been used to investigate auditory temporal resolution at presumably higher central levels in infants. MMN is generated primarily in auditory cortex to infrequent deviant stimuli (containing gaps in a gap detection task) in comparison with frequent standard stimuli (no-gap). MMN is measured at the scalp between 150-250 ms after stimulus onset as a greater brain electrical negativity in EEG activity evoked by the stimulus in this case better detected over frontal sites, with greater positivity detected at mastoid sites. MMN detection thresholds at 2000 Hz in 6 month-old infants were similar to those of adults (Trainor et al., 2001). However, no clear MMN were observed in 2-month-olds (Trainor et al., 2003).

d. Cochlear maturation

Cochlear function, which includes characteristic frequency selectivity and hair cell function, plays an important role in auditory sensitivity and frequency resolution enhancement. Distortion product otoacoustic emissions (DPOAE), which measure the intermodulation distortion products generated within the cochlea when two tones are presented simultaneously, provide a noninvasive tool to examine the development of cochlear function. Cochlear function in term newborn infants is similar to adults for tones with low frequency (1500Hz), but not adult-like in premature infants (Abdala, 1998, 1999, 2000). On the other hand, cochlear function immaturity has been found in both premature and full-term newborns when recorded with tone of higher frequency (6000Hz) (Abdala, 2003). Recent work showed that this discrepancy at 6kHz could be due to developmental differences in the middle ear (Abdala et al, 2007) or in the ear canal (Keefe & Abdala, 2007) between infants and adults.

In summary, available data using psychophysical methods suggests that (1) cochlear function at lower frequencies is mature at birth. Premature infants exhibit immaturity in this function; (2) absolute thresholds and intensity discrimination is improved postnatally; (3) some aspects of frequency resolution is adult-like by 6-months of age. Younger infants are poorer in detection change in higher frequencies region; and, (4) based on psychophysical gap detection paradigms, temporal resolution performance is immature at 3 months of age, although ABR thresholds to gaps is adult-like in 3-month-old infants, suggesting the maturity of temporal resolution mechanisms at least at the brainstem level. This review also suggests that relatively little is known about these fundamental auditory capacities in younger infants, especially newborns. However, available data indicates that hearing threshold in newborn infants is about 10-15dB higher than that of adults.

2. Auditory perception of complex stimuli

a. Perception of maternal speech

Newborns exhibit preferences to their own mother's voice. Using a conditioned sucking technique where infants initiate a burst of sucks during one of two auditory stimuli, DeCasper and Fifer (1980) reported that newborns suck differentially when listening to their own mother's voice than when listening to the voice of an unfamiliar mother. When given a choice between a low-pass filtered version of their mother's voice and an unfiltered version, newborns vary their sucking rates, interpreted as preferences to the low-pass filtered version (Fifer & Moon, 1989). Moreover, Spence and Freeman (1996) have shown that newborns prefer their own mother's voice over that of another female when both voices are low-pass filtered, but not when they are whispered. These results suggest that intonation or the prosodic information carried by the fundamental frequency in low-pass but not whispered speech is important for voice recognition.

Interestingly, these data indicated that the filtered version has a spectral content similar to sound contents available in utero. Using hydrophone recordings, Querleu et al (1989) have shown that both internal (maternal) and external sounds of high intensity and low frequency are present in the amniotic fluid surrounding the fetus' ears. Similarly, this early experience is reported in the preference listening of newborns to familiar stories with different rhythmic structures, as read aloud repeatedly by their mother during the final weeks of pregnancy (DeCasper and Spence, 1986). Taken together, these findings suggest an influence of auditory experience in the womb.

Special characteristics of infant-directed (ID) speech in the mother's voice are relevant here. Systematic examination on the effects of varying pitch, amplitude and rhythmic features on infants' preferences to ID speech has revealed the critical difference as relying on dynamic pitch characteristics (Fernard and Kuhl, 1987).

Although there is evidence for the specific role of auditory experience on voice preferences in newborns, there also is evidence against it. For example, in the absence of prenatal exposure to ID speech (Cooper & Aslin, 1990) or ID singing (Masataka, 1999), newborns show clear preferences for these sounds. Thus, there are some acoustic characteristics of sounds that may be intrinsically preferred by infants in the absence of any inducing experience.

b. Tonal sequence discrimination and melody perception

Ability to discriminate and categorize rapid sequential sound patterns is essential for melody perception. A fixed sequence of tones that varies in frequency comprises a simple melody. Trehub (2001) has reviewed melody perception in infants. Five to 10-month-olds can discriminate one melodic pattern from another (Chang and Trehub, 1977; Trehub, Bull & Thorpe, 1984). They appear to differentiate melodies based on the global direction of tone

intervals, or pitch contours. Infants found it more difficult when presented with changes in tone intervals that preserved the pitch-contour (a transposition of the melody) (Trehub, Thorpe and Morrogiello, 1987; Morrongiello et al, 1985). However, infants could detect interval changes with small-integer spacing tones (Cohen, Thorpe and Trehub, 1987; Trainor & Trehub, 1993). Besides pitch-contour, rhythmic cues have also been shown to be a basis for sequence discrimination in 7-to 9-month-olds who can discriminate changes in grouping of tones based on a pause separating two groups of tones (rhythmic cues) (Trehub & Thorpe, 1989). Thus, discrimination of tonal sequence and melody perception has been observed as early as 5-month-olds. Pitch contour seems to be the most salient dimension in infants' melody perception. This important ability in auditory perception has not been investigated at earlier ages.

c. Pitch perception of complex tones

Pitch perception is a crucial basis for speech intonation perception and melody perception. Pitch is defined as "that attribute of auditory sensation in terms of which sounds may be ordered on a scale extending from low to high. Pitch depends mainly on the frequency content of the sound stimulus, but it also depends on the sound pressure and the waveform of the stimulus". (American National Standards (ANSI), 1994).

Sounds in the natural environment almost always involve complex tones. A complex tone consists of more than one frequency components. The lowest component of a tonal complex is called its fundamental frequency (F0). Frequency components with integer multiples of F0 are found in harmonic tonal complexes. Inharmonic complexes, on the other hand, are composed of components mistuned from harmonic relationships (Hartmann, 1997). An overview of critical issues in literature of pitch perception of complex tones is presented below.

(1) Overview of research in pitch perception

Historically, two major types of theories had been developed to explain the mechanism of pitch perception, "place" theories and "timing" theories. Place theories consider pitch to stem from place (or spatial aspects) of excitation pattern on the cochlear basilar membrane. Timing theories, on the other hand, attribute pitch perception to timing (temporal or periodicity aspects) of auditory neural firing. For a thorough review of different pitch perception theories, see de Cheveigne, 2005.

These perspectives also have been used to explain pitch perception of complex tones with "missing fundamental" (MF), or "low pitch". Pitch percepts were first explained as derived from the F0 of the sound based on the ear's capacity to perform frequency analyzer capacity (Ohm, 1843). This place theory was challenged when August Seebeck (1841) demonstrated that an acoustic stimulus, with very weak energy at F0, still evoked a strong pitch equivalent to the fundamental component. This was the first evidence the perception of MFs. Moreover, further experiments showed that the perceived pitch at F0 did not alter after removing F0 completely from the stimulus (Schouten, 1938), or masking the band around F0 with noise (Licklider, 1956). Schouten called this pitch percept from higher components as "residue pitch". In favor of Ohm's theory, Helmholtz (1877), and later Fletcher (1924) proposed that nonlinear distortion products generated by acoustic stimuli were the basis of this low pitch perception . That is, interaction between neighboring component frequencies could "reintroduce" the frequency of the "missing" F0 on the BM. Schouten (1938) disputed this distortion hypothesis. He demonstrated that the distortion product measured at the MF frequency was weak. Additionally, he also proved that residue pitch was not due to the perception of difference tones corresponding to the component frequency intervals. He created inharmonic tonal complexes by shifts in the frequency of

harmonic components, yet the component frequency intervals (equivalent to F0 in harmonic relationship) remained unchanged. Low pitch perceived changed in the direction of the frequency shifts (pitch-shift). He proposed that the perceived pitch was the result of periodicity detection of auditory neurons' firing in synchrony with the envelope fluctuations of the cochlea-filtered waveform to the stimulus. Subsequent experiments by de Boer (1956, 1976), in which pitch-shift paradigm was studied in a quantitative detailed manner, further suggested two possible mechanisms underlying low pitch. In the inner ear, acoustic inputs go through a bank of overlapping auditory filters, or critical bands. The outputs of the filters for low harmonics are sinusoidal. For pitch derived from purely spectral information, the relevant information could be extracted through some form of template-matching operation. For non-aurally-resolved complexes, synchronization to the waveform's "pseudo-period" (interval between approximate repetitions of the waveform modulation pattern) could be a basis of low pitch. It was observed experimentally that as the degree of inharmonicity increased, ambiguity for pitch increased.

An "existence region", where listeners can perceive a tonal low pitch, has been established, using amplitude-modulated signals (Ritsma , 1962). This limit is restricted to relatively low fundamental frequencies (below 800 Hz) and to relatively low frequency, spectrally resolvable components. Moreover, Plomp and Ritsma (1967) independently showed that low components have a greater influence on pitch than higher components. The most dominant region for conveying low pitch lies between the third and the fifth harmonics, which are spectrally resolvable components.

In varying spectra of tonal complexes, Patterson (1973) found that low pitch remains constant as long as the spectrum has the same lowest component. This pitch invariance is often termed perceptual constancy. The number of components can range from 2 (Smoorenburg, 1970)

to 12 (Patterson, 1973), however, the pitch salience of the complexes decreases with very small numbers of components

This finding and others (Mathes and Miller, 1947; Licklider, 1955; Ritsma and Engel, 1964; Moore, 1977) didn't fit well with the temporal fine-structure model, because varying the phase relations among components of tonal complexes didn't change low pitch. A model of pattern recognition was proposed (Wightman, 1973;Goldstein, 1973; Terhardt, 1974), which focused on the aurally resolved portion of the spectrum. In this model, spectral profiles are derived from neural peripheral auditory inputs, and followed by central pattern-matching mechanisms (see Greenberg, 1987; Clarkson, 1992 for reviews). Shamma and Klein (2000) proposed a model of that this pattern matching mechanism based on cochlear filtering and coincidence detection in-utero when the fetus is exposed to various inharmonic sounds associated with maternal biological processes.

The modern view of pitch theories, the spectro-temporal model, includes both spectral and temporal mechanisms (Moore, 1982, 1989; Moore and Glasberg, 1986; Patterson, 1987; Meddis and Hewitt, 1991) (see Moore, 1997 for a review). In this model, the initial place/spectral analysis in the cochlea is followed by an analysis of the time pattern of the waveform at each place or of the neural spikes evoked at each place. In the model proposed by Moore (1982, 1989), acoustic inputs go through a bank of overlapping auditory filters, or critical bands. The outputs of the filters for low harmonics are themselves sinusoidal, whereas the outputs of higher harmonics respond to the interaction of several harmonics, which have repetition rates corresponding to the sums of inputs. In the following stage, outputs from the auditory filters are transduced into neural impulses. The temporal pattern of neural firing reflects the temporal structure of the cochlea-filtered waveform. The next stage is an analysis of spike

intervals. This is achieved through summing time intervals in different channels over time (autocorrelation of neural firing). The resulting autocorrelogram exhibits peaks, the largest of which corresponds in most cases to the perceived pitch of sound. Cariani & Delgutte (1996) had provided the most complete neurophysiological data constructed from interspike interval distributions of auditory nerve fibers corresponding to pitch percepts. In general, the most common time interval found corresponds to the period of the fundamental component. However, this unitary mechanism is challenged by another point of view (Grimault et al., 2002). Using a transfer-of-learning approach, Grimault and coleagues showed evidence of two pitch encoding mechanisms depending on the aural-resolvability of the harmonic tonal complexes.

In contrast to models based on peripheral auditory mechanisms, a central origin was suggested from an observation of impaired low pitch synthesis in people with auditory cortex damage (Zatorre, 1988). In support for this position, Patel and Balaban (2001), using magnetoencephalographic recordings, showed that MF pitch perception is reflected in the timing of stimulus-related cortical activity. Recently, Bendor and Wang (2005) reported the finding of neurons in the auditory cortex of marmoset monkeys that respond to both pure tones and MF of harmonic complex sounds with the same F0. Interestingly, the location of these neurons in marmosets is compatible to human pitch-processing areas suggested in studies of human auditory cortex (Zatorre, 1988; Patterson et al., 2002; Penagos et al, 2004).

(2) Evidence of infants' ability to discriminate the pitch of complex tones

A series of investigations on low pitch perception in 7-8 month-old infants has been reported using a conditioned head-turning paradigm (Clarkson, 1985; 1995). In these studies, a number of spectrally different tonal complexes were presented that contained varying harmonic components but signaled the same two pitch categories. After learning the basic pitch

discrimination, the infant learned to categorize spectrally different tonal complexes according to the pitches signaled by their fundamental frequencies. Finally, they heard tonal complexes that signaled the same pitch categories but for which the fundamental frequency was removed. These 7-8 month-old infants showed evidence of discriminating pitch differences as well as perceptual constancy for the pitch of harmonic complexes. They could discriminate the harmonic complexes according to their pitch categories even when fundamental frequencies had been removed. However, infants showed difficulties in synthesizing low pitch percepts in inharmornic tonal complexes, decreasing with the degree of increasing inharmonicity, findings similar to what is seen in adults. These studies point to the importance of spectral information for pitch perception in infants (Clarkson & Clifton, 1995).

Using noise masking of pure tones and tonal complexes, Montgomery and Clarkson (1997) found that 7-8 month-old infants, also like adults, successfully discriminate pure tones when combined with a high-frequency noise but not when combined with a low-frequency noise in the same frequency range as the pure tone. Infants, as did adults, also learned to categorize complexes based on the pitch of the missing fundamental when stimuli were combined with a low-frequency noise in the range of the missing fundamental, but failed to do so when combined with the high-frequency noise which covered the harmonics themselves. These results also provided evidence for the role of spectral cues. Furthermore, the fact that infants still heard the pitch of the missing fundamental in the presence of the low-frequency noise indicated that they did not rely on the combination of tones to perform the task.

Clarkson and Rogers, 1995, emphasized the influence of frequency spectra on the development of pitch perception . Like adults, the strength of pitch for infants was greater for

sounds containing relatively low-energy, spectrally resolvable components than for those having only high-frequency energy, spectrally-unresolvable components.

In summary, the available data on infants' pitch perception in 7-8 month olds provides evidence of an ability to discriminate pitch. Moreover, spectral cues are shown to be important for infants pitch perception performance. As seen in the above review, the conditioned head turning procedure has been extensively utilized to examine pitch perception behaviorally in young infants. However, behavioral methods do not address the neurobiological bases of pitch perception. Furthermore, the dependence on attention and requirement for a degree of motor skill required for the response make the technique more difficult to use and the data harder to interpret in very young infants. This may be a reason for the lack of data at earlier ages, especially during the neonatal period when a conditioned head turn may not be possible to obtain..

The frequency following response (FFR), with its characteristic features mirroring the frequency contents of the stimuli, reflected in the phase (timing) and magnitude of the scalp-recorded responses (Marsh et al., 1974; Smith et al., 1975; Sohmer et al., 1977 in Hall, 2006; Batra, Kuwada & Maher, 1986; Krishnan & Parkinson, 2000), has been shown to be appropriate for the examination of pitch extraction (Greenberg et al., 1987; Galbraith, 1994; Krishnan et al., 2004). Galbraith, 1994, pointed out the utility of using MF stimuli. He suggested that they provide "…unique opportunities to study sensory coding and higher perceptual processing" since the fundamental frequency does not exist in the frequency spectrum of the stimulus. In regard to neural mechanisms of pitch perception, it seems reasonable to hypothesized that if pitch processing would be compromised by early brain injury presumed to corrupt the integrity of the auditory system, then the functional processes of the different types of auditory neurons and their

different pathways could be affected. Since perinatal brain injury is common in premature infants.

II. Brain insult in high-risk neonates

Progress in prenatal, perinatal and postnatal care has continued to improve the survival rate of extremely immature and sick infants dramatically, increasing the number of brain injury infants with high-risk for developmental sequelae. During the neonatal period, neuropathology of brain injury is more likely to involve subcortical regions. The effect of subcortical dysfunction has been shown to correlate to perceptual and cognitive deficits. A brief review of documented subcortical dysfunctions in high-risk neonates will be provided. Since prematurity creates one of the highest potentials for brain injury and developmental sequelae, CNS neuropathology and neurodevelopmental deficits in premature infants will be discussed in more detail.

A. Subcortical dysfunction in high-risk neonates

Each year, approximately 350,000 low birth weight (LBW, birth weight <2500g) infants are born in the United States (Guyer et al., 1995). Infants of very low birth weight (VLBW, birth weight <1500g) account for 1 percent of all annual births (about 40,000 births per year). Of LBW infants, 70% are premature (Guyer et al., 1995). A premature infant is defined as one born at or before the 36^{th} week of gestation. The survival rates of premature infants continue to improve due to advances in neonatal medicine. In addition, there has been a reduction in the occurrence of known neonatal neurosonographic correlates of adverse outcomes, i.e., severe intraventricular hemorrhage (Perlman, 2001; Cooke, 1999; O'Shea et al., 1998).

However, there is no indication of any decrease in the suspected involvement of insult to the brainstem and other subcortical regions (Volpe, 2001), regions difficult to visualize by cranial ultrasound (CUS) (Levene et al., 1983), the most common method to view the brain

structure of neonates. In very low birth weight or severely asphyxiated neonates, CNS damage tends to occur in subcortical regions as they have the highest metabolic rate and blood supply, combined with the most frail capillary system. Moreover, Volpe (1995) points out that neuronal pathology can be detected at pontine levels of the brainstem in as much as 71% of infants with IVH. In both preterm and term infants, CNS injury produced primarily by hypoxia (e.g., hemorrhage, infarct, encephalopathy) often occurs to subcortical structures (Fawer et al., 1983; Volpe, 2001). Measurements of blood flow (Landau et al., 1955) as well as baseline uptake of deoxyglucose, an indicator of neural activation (Sokoloff, 1981) have pointed to the inferior colliculus, a region known to process auditory information, as being particularly activivated in the premature infant. Unsurprisingly, in hypoxic-ischemic events in these high-risk infants, this site is one of the most vulnerable for brain insults. As might be expected, since perinatal brain injuries typically involve areas in close proximity to auditory areas or auditory pathways, it has been shown that compromise to CNS functional integrity as correlated to IVH can be assessed by effects on ABR measurements (e.g., Karmel et al., 1988; Edwards et al., 1985; Hecox et al, 1981; Henderson-Smart et al., 1983; Ito, 1984; Stockard et al., 1983). Such adverse events may affect neural impulse conduction through the brainstem, causing absent or delayed component responses or decreased component amplitude ratios (Majnemer, Rosenblatt & Riley, 1990). Although providing different forms of information, agreement between CUS and ABR is high, between 78%-and 86% (Fawer et al, 1983; Karmel et al, 1988). The disagreements probably "reflect substantive differences in regional CNS injuries, their differential courses of recovery or the distinction between structural and functional integrity of the CNS" (see Karmel, Gardner, Kapadia & Harin, 1998).

In addition, modulation of arousal and attention, suggested to be mediated by subcortical structures, has been correlated with perinatal brain injury (see Gardner & Karmel, 1983; Karmel et al., 1991). Follow-up studies that examine different aspects of development ranging from cognition to fine and gross motor involvement have indicated a strong relation between CNS problems and poor outcome in these areas (e.g., Fawer & Calame, 1991; Graziani et al, 1985; Hack et al, 1994; Jongmans et al, 1997; Prechtl et al, 1997; Sostek, 1988; Wallace et al, 1995).

B. Prematurity, risk of brain injury, and neurodevelopmental sequelae.

1. Prematurity and intraventricular/parenchymal hemorrhage

Approximately 33-50% of all VLBW infants develop subependymal and intraventricular hemorrhage (IVH) in the immediate postnatal period. IVH primarily originates in the subependymal germinal matrix (GM), a subcortical cellular region located adjacent to the lateral ventricles, with many delicate blood vessels making it vulnerable to hemorrhage. GM-IVH was initially classified by Papile et al. (1978) into four grades: Grade 1, with hemorrhages confined to the periventricular GM, Grade 2, with hemorrhages extending into the ventricles but without ventricular dilatation, Grade 3, with ventricular dilatation, and Grade 4 with hemorrhages extending into the cerebral parenchyma. Ventricular dilatation following a severe periventricular hemorrhage leads to progressive hydrocephalus in some cases (Volpe, 2001). The severity of CUS abnormality has been further classified in regard to the degree of tissue loss (Prechtl, 1997). Karmel et al. (1990) have combined criteria into a 3-category ordinal variable reflecting increased severity of CNS injury: 1) slight: GM hemorrhage alone or with tiny cysts, IVH alone (Papile grade I); prominent choroids; tiny choroid cysts; questionable abnormality; 2) mild-moderate: IVH (Papile grade II-III) alone or with cysts; ventriculomegaly </= 5mm; 3) strong-severe: IVH grade III-IV; ventriculomegaly >5mm; periventricular or parenchymal

leukomalacia, hyperechoic echogenicity, or multiple cysts >3mm; subarachnoid hemorrhage; cerebral edema >48 hours with IVH or PVL; hydrocephalus >10mm; hemorrhage or dilatation of IIIrd or IVth ventricle; large or multiple porencephalic cysts, parenchymal hemorrhage or infarct; seizures requiring treatment. Ventricular dilation in CUS may represent cerebral atrophy, and is often associated with periventricular leukomalacia (PVL). PVL refers to necrosis of the white matter adjacent to the lateral ventricles, which leads to the formation of cysts, subsequent gliosis, and ventricular dilatation due to tissue loss. As a white-matter disorder, PVL is considered a major risk factor for neuromotor and neurosensory handicaps (Volpe, 2001).

The GM provides a source of glioblasts which will develop into oligodendroglia and astrocytes in the third trimester. A GM hemorrhage is likely to damage the matrix and thus its glial precursor cells. These glial precursor cells are necessary for astrocytic development. Evrard and colleagues (Volpe, 2001) have shown that astrocytes destined for supragranular cortical layers originate and migrate after the occurrence of neuronal migration (by the 24th week of gestational age) and are crucial for normal organizational development of the supragranular cerebral cortex. Thus, astrocytic precursors destroyed by IVH could set the stage for later cortical developmental disturbances. Moreover, in vitro finding using quantal analysis and microscopy revealed the role of astrocytes in inducing and stabilizing synapses (Ullian, 2001; 2004). These data might help to explain disturbances of synaptogenesis following the loss of glial precursors.

The relation of glial precursors to subsequent impairment of myelination caused by a loss of oligodendroglia is not clear. The frequent association in infants with IVH of periventricular white matter injury secondary to periventricular white matter hemorrhagic infarction, periventricular leukomalacia (PVL), and posthemorrhage hydrocephalus makes this issue

difficult to resolve. MRI studies of premature infants after the neonatal period do not suggest that IVH alone results in impaired myelination (see Volpe, 2001)

2.Prematurity and neurodevelopmental sequelae

Although there has been a reduction in the occurrence of known neonatal neurosonographic correlates of adverse outcomes, i.e, severe IVH, it has become apparent that a large number of VLBW infants exhibit neurobehavioral problems in the absence of cerebral palsy when follow-up has extended into school age and adolescence (e.g, Hack & Fanaroff, 1999; Hapieski & Evankovitch, 1997; Stjernqvist & Svenningsen, 1999). Because of the practice of using birth weight, rather than gestational age, when reporting outcomes, the most common examined outcomes in the premature population are estimated by birth weight. This poses a problem in relating CNS development and outcomes since maturity of the infant has a major effect on normal neurodevelopmental sequelae. About 30 to 50 percent of these children's academic achievements are in a subnormal range, and 20-30% exhibit attention-deficit hyperactivity disorder (see Perlman, 2001 for a review). The main factor that may contribute to these problems is the vulnerability of the premature brain during a critical period of development. Unlike full- term infants, the available data has suggested that cortical neuronal injury is not the crucial occurrence. Rather, the underlying cause of deficits in premature infants might be a lasting disturbance of the organization of the brain. Gardner, Karmel and colleagues in their follow-up study suggested that neonatal brain injury evident on CUS and/or ABR disrupts the normal modulation of attention to differing degrees of stimulation in different arousal conditions. This regulation deficit "should not necessarily lead to gross cognitive or motor delay in the first years of life, but disrupts fine-tuning of regulatory capacities that require a smooth hierarchical organization of the brain". Thus, difficulties in the regulation of basic

subcortical physiological functions such as arousal, attention, sleep, feeding, or self-soothing during the neonatal period likely result in emergence of attention deficit or hyperactivity disorders later in life (Gardner, Karmel, 1991, 1998, 2002, 2003).

The adverse consequences of prematurity on neurodevelopment are evident from an early age. Ross et al. (1992) found that premature infants (28-32 week) with mild (Grade 1 or 2) intraventricular hemorrhage (IVH) on the cranial ultrasound (CUS) performed poorly on tests of infant cognition and habituation or novelty preference when tested at 10-months-corrected age, compared with a premature group without evidence of IVH. Both these premature groups were less successful than the full-term infants on a test of memory for location. Similar differences were found at 2 years of age on tasks of delayed memory and the ability to change response set (Ross et al., 1996).

In a longitudinal study on outcomes in infants and toddlers with birth weight less than 1600g, Landry and colleagues (1993) demonstrated that these children had poorer mental and motor development in comparison to term controls from 6 to 36 months of age. The poorest performances were found in those with severe IVH and chronic lung disease. They showed a slower rate of development in mental and expressive language skills and social initiation. Follow-up of the VLBW sample during the school-age years suggests continued sequelae, including deficits in cognitive skills, behavior, and academic achievement (e.g, Hack et al., 1995; Whitfield, Grunau & Holsti, 1997; Botting, Powls & Cooke, 1997; Breslau et al., 1996; Rosenbaum et al., 1995; Sommerfelt, Ellertsen & Markestad, 1993; Klebanov, 1994) (see Taylor, Klein & Hack, 1998 for a review). Poorer outcomes were reported in premature children than in term-born controls, even after the exclusion of individuals with neurosensory impairments or subnormal overall cognitive abilities (e.g, Hack et al, 1992; Luoma et al., 1998; Waber &

McCormick, 1995). In a study by Frisk and Whyte (1994), selective cognitive outcomes were examined in 6-year-old children born less than 1000g birth weight, including three sub-groups: no lesions on cranial US, mild lesion (grade 1 or 2 IVH) or severe lesions (grade 3 or 4 IVH) compared to full-term controls. The mild–lesion group performed poorly on sentence comprehension and verbal working memory. The severe-lesion group showed more pervasive deficits as relative to term controls. Yet, like the previous group, they were not impaired on measures of category fluency, list learning or rate of forgetting. For both lesion groups, impairments in the ability to follow verbal instructions were observed on tasks involving complex verbal commands. Monset-Couchard, De Bethman, and Kastler (1996) also described increased rates of mild developmental, learning, and behavior problems over time in less than 1000g- birth weight children in early childhood.

In summary, a vast literature addresses the high-risk for adverse developmental sequelae in various areas of development in premature infants. This does not include effects of other types of perinatal brain injury, i.e. that of asphyxiated full-term infants, which also may involve subcortical dysfunctions. However, the focus on basic auditory processing in premature infants, such as the processing of complex tones would allow two questions to be examined simultaneously. First, examining pitch processing correlates in premature infants at different gestational ages during the perinatal period would provide information on the early development of critical auditory processing capabilities. Second, given the high proportions of developmental sequelae, including selective cognitive and language deficits, in premature infants, understanding the types of processes that may be compromised by brain insults would be invaluable in the search for appropriate early interventions.

III. Auditory brainstem revoked responses (ABR)

ABR have been to be shown to be useful tools for assessing functional integrity of the CNS during the neonatal period and subsequent early life (e.g., Karmel et al., 1988; Edwards et al., 1985; Hecox et al., 1981; Henderson-Smart et al., 1983; Ito, 1984; Stockard et al., 1983). This assessment, using primarily wave I, III, V and III-V interval information can serve as an early indicator of brain injury in neonates (Karmel et al., 1998) because of the strong association of these ABR parameters with confirmed CNS injury.

The ABR reflects electrical events generated within the auditory pathways from the eighth nerve to the diencephalon. These electrical events are recorded differentially between a positive electrode on the vertex, a negative electrode on the mastoid and a forehead serving as a ground. The low-level brainstem signals are embedded in the recorded signals and are thus enhanced using signal averaging. The auditory stimulus is usually a rectangular click administered at a relatively rapid rate. The response typically consists of seven vertex-positive components, designated consecutively by Roman numerals I-VII.

Studies in animals indicate that the waves are derived from sequential activation of the major components of the auditory pathways (see Hall, 1992). With regard to the site of ABR generators, there is a discrepancy between animal findings and recordings from humans. The simplistic schema in clinical practice usually associates a single structure or region in the ascending auditory system with each successive major ABR component. Thus, wave I presumably represents activity of the eight nerve; wave II, cochlear nuclei; wave III, superior olivary complex; wave IV, lateral lemniscus; wave V, inferior colliculus. However, Moller demonstrated that in humans, ABR wave I and II are generated from distal and proximal eighth nerve, respectively, as observed in intracranial recordings (see Hall, 1992). Later ABR

components (waves III, IV, and V) are suggested to reflect combined or "compound" neural activity from axonal pathways in the auditory system, in specific, the cochlear nucleus, superior olivary complex, lateral lemniscus and the inferior colliculus (reviewed in Moore, 1987) . The origins of wave VI and VII are not clear, but are suggested to be from the thalamus (medial geniculate body and thalamic projections to primary auditory cortex) (Stockard & Rossiter, 1977; Hashimoto et al., 1981). Yet, Moller and colleagues attribute these peaks to continued synchronous firing of neurons in the inferior colliculus (see Hall, 1992). Regardless of their origins, each of the ABR components requires the integrity of anatomically descrete and diffuse systems comprising a limited set of brainstem neurons, their axons, and the neurons on which they terminate (Zaaroor & Starr, 1991a,b).

Since ABR are well defined in newborns and are not affected by sleep, this technique has been used as one of the standardized tests in hospitals for newborn hearing screening. These far-field evoked potentials have also been employed as a neurophysiological approach to the assessment of brainstem integrity, especially on an NICU and have been used to predict early brain insult (Karmel et al, 1988; 1998).

Steady decrease in interpeak intervals, especially the I-III and I-V interpeak intervals, in serial ABR is a sign of maturation in the ABR (Despland & Galambos, 1980; Fria & Doyle, 1984; Inagaki et al., 1984), whereas rapid decrease is likely to reflect recovery from insult (Karmel et al., 1988). Interpeak latencies reflect brainstem conduction time, which is dependent on axonal conduction and synaptic delay (Ponton, Moore & Eggermont, 1996). Although in premature infants, the ABR can be recorded first at 28-29 week corrected age (e.g., Despland & Galambos, 1980; Inagaki et al., 1984), in our lab, we found that ABR recordings could not reliably be obtained until 32 week corrected age. This is in line with other studies, in which

detection of various waves of the ABR reaches 80-100% at about 30 to 32 week gestational age (Fawer & Dubowitz, 1982; Ken-Dror et al., 1986; Krumholz et al., 1984; Amin et al., 1999).

IV. Frequency Following Responses (FFR)

FFRs, first described by Worden and Marsh (1968), are far-field auditory evoked responses to continuous tones. The recorded potential mirrors the frequency content of the acoustic stimuli. The source of this potential has been suggested to be at the rostral brainstem in humans based on its latency and on lesion studies (Marsh et al., 1974; Smith et al., 1975; Sohmer et al., 1977 in Hall, 2006; Batra, Kuwada & Maher, 1986). The locus of generation is still controversial (Gardi, Merzenich & McKean, 1979a; Chimento & Schreiner, 1990; Galbraith et al., 2000; John & Picton, 2001; Boettcher et al., 2002). Although the underlying mechanism of the FFR remains unclear, it is thought to include contributions from hair cell dynamics, cochlear mechanics, and phase-locked coding of neural activity to low frequency signals (below about 2 kHz) in the auditory system.

The advantages of FFR over click-evoked ABR are the ability to examine responses to continuous, more naturalistic stimuli, such as in speech (Krishnan, 2002; Krishnan et al., 2004) as well as in non-speech complex sounds (Greenberg et al., 1987; Wile & Balaban, 2007). Furthermore, the FFR is more frequency-specific because its individual components are spectrally separable in the response. In addition, FFR responses have been shown to be robust even when background noise is introduced (Russo et al., 2004; 2005).

Auditory steady-state responses can be recorded noninvasively in infants during the neonatal period (Gardi, Salamy & Mendelson, 1979b; Levi, Folsom & Dobie, 1995; Maurizi et al., 1990; Rickards et al., 1994). Since the crucial feature of FFR is that it mirrors the frequency contents of the stimuli, reflected in the phase (timing) and magnitude of the scalp-recorded

response, it has been shown to be appropriate for the examination of neural encoding of time-variant frequency (Krishnan & Parkinson, 2000), pitch contour (Krishnan et al, 2004; Swaminathan et al., 2008) as well as the pitch of a missing fundamental (MF) (Greenberg et al., 1987). In their study, Greenberg et al. showed evidence of scalp-recorded FFR reflecting physiological processes underlying the major psychophysical features of pitch of complex tones, which are: 1) existence of a component corresponding to the MF in FFR spectra; 2) the response is impervious to masking by low frequency noise; 3) FFR to the MF is not the result of neural synchronization to the waveform envelope modulation pattern of the tonal components; 4) FFR response to inharmonic complexes is comparable to the observed psychophysical "pitch shift".

There is no published research investigating pitch processing in neonates and the earliest age pitch perception has been investigated is 4-months where a heart rate change paradigm gave negative findings (Bundy, 1979). There is evidence that MF perception is a taxonomically pervasive phenomenon. Studies in fish, birds and mammals suggest that periodicity pitch perception may be a general process in vertebrate hearing (Cynx & Shapiro, 1986 in Gabraith, 1994 ; Tomlinson & Schawart, 1988 in Winkler,1996) and would suggest the possibility of MF perception existing early in human infants. With regard to neural coding mechanisms, there is evidence that MF coding is mediated at subcortical levels. Pantev et al. (1989), investigating the tonotopic organization of the auditory cortex by means of evoked neuromagnetic measurements suggested that "the tonotopic organization of the primary auditory cortex reflects the pitch rather than the frequency of the stimulus, and that the pitch formation process must take place in subcortical regions". Whether the magnetic counterpart of the auditory N1 event-related potential using in this study represents a pitch code or not (see Crottaz-Herbette & Ragot, 2000; Lutkenhoner, Lammertmann & Knecht, 2001; Winkler, Tervaniemi & Naatanen, 1996), the

notion that subcortical contributions to pitch coding are reflected in cortical responses is widespread (e.g., Meddis & Hewitt 1991; Langner 1992, Winter, Wiegrebe, Patterson 2001). Galbraith (1994) utilized two-channel (vertical and horizontal) brainstem FFR recordings and ABR to study MF coding along the auditory pathways in human adults. Horizontal channels were recorded differentially between the two ears, while vertical channels were recorded from the active electrode in vertex referenced to the left ear. He demonstrated robust FFR in the vertical channel occurring at latencies consistent with ABR waves IV-V and MF frequency representation in the brainstem auditory pathway. The absence of FFR to MF in the horizontal channel supposedly reflected the dominance of neural activity from the auditory nerve to the ipsilateral cochlear nucleus, comparable to ABR wave I-III, and was interpreted as evidence that MF is not directly derived from peripheral coding. This supported the point of view that MF detected is not solely resulted from the non-linear distortion products generated along the basilar membrane.

V. Otoacoustic emissions (OAE)

OAEs are small acoustic signal generated in the hair cells as they participate in the active filtering process of the cochlea that enhances low-level sensitivity and frequency selectivity of the basilar membrane (BM). Motion generated by the hair cells modifies cochlear mechanics, which in turn produces mechanical energy which is transmitted back along the BM and out through the middle ear to the ear canal. Because OAEs are generated solely within the cochlea and are recorded noninvasively, they offer a window into human cochlear function. Due to relatively rapid data collection, OAE is used currently as a hearing screening procedure in neonates. Distortion product OAE information, if available, is helpful in determining the role of the cochlea in generating neural signals detected in FFR recordings.

VI. Scope of the study

The literature review has shown that 1) extensive research addresses high-risk developmental sequelae in premature infants and infants with perinatal brain insults, but that, 2) there is limited research on auditory processing of complex tones during the newborn period related to its development either in CNS-injured infants or in infants where CNS injury has been ruled out.

Thus, the focus of this study is on processing of complex tones, a basic auditory processing in premature infants varying as a function of gestational age, with and without brain insults documented during the neonatal period prior to their hospital discharge from the NICU.. This study design age crossed with CNS insult allows two questions to be examined simultaneously. First, the design will allow examination of pitch-related information-processing correlates to differences in CNS maturation assumed to vary as a function of age at test during the perinatal period thereby providing new information on the early development of critical auditory-processing capabilities. And, second, given the high proportions of developmental sequelae, including selective cognitive and language deficits, in premature infants and infants with perinatal brain insults, the design will enhance understanding of the types of processes that may be compromised by brain insults, information that might be usful in the development of appropriate early interventions.

Thus, we hypothesized that:

1. Processing of complex tones emerges late during the newborn period at term age.. Alternately, this processing capability already exists in premature infants when tested at any time prior to hospital discharge but before 37 weeks gestation.

2. Pitch-related information processing relies on the integrity of the auditory pathway. Brain insult in the perinatal period has been shown to be highly likely to effect subcortical structures, including auditory brainstem. If there were delays in or problems with pitch processing in brain insulted infants, compared to development in non-brain insulted infants at any age, in the absence of peripheral disturbances, strong evidence would be obtained supporting a CNS mediation of the development of pitch-related information processing.

CHAPTER 2- MATERIALS AND METHODS

I. Subjects

A total of 128 infants (boys=55%, mean gestational age (GA) at birth=34 weeks, range 23-41 weeks) born at Richmond University Medical Center in Staten Island (RUMC) were studied cross-sectionally during the perinatal period. Postconceptional age (in weeks) at test (PCA) (calculated as the GA + (# days after birth/ 7)) was 36 weeks +/-2.5 weeks, (range 32-46 weeks).

A. Inclusion criteria

Premature and full-term newborn infants with or without any indication of perinatal brain injury were included. Indications of brain insult (BI) were: structural abnormal cerebral US (CUS) findings and/or functional abnormality in ABR defined by an ABR component latency pattern known to relate to CNS injury (Karmel et al., 1988, 1998). Non-BI infants were defined as those infants with normal CUS and ABR or normal ABR only, but too healthy to have a routine clinical CUS assessment ordered clinically. Information on GA as determined by a medical examination was obtained from the clinical record.

1. Abnormal CUS

The abnormality and severity of CUS was classified as follows 1) slight: GM hemorrhage alone or with tiny cysts, IVH alone (Papile Grade I); prominent choroids; tiny choroid cysts; questionable abnormality; 2) mild-moderate: IVH (Papile Grade II-III) alone or with cysts; ventriculomegaly </= 5mm; 3) strong-severe: IVH grade III-IV; ventriculomegaly >5mm; periventricular or parenchymal leukomalacia (PVL), hyperechoic echogenicity, or multiple cysts >3mm; subarachnoid hemorrhage; cerebral edema >48 hours with IVH or PVL; hydrocephalus >10mm; hemorrhage or dilatation of IIIrd or IVth ventricle; large or multiple porencephalic cysts, parenchymal hemorrhage or infarct; seizures requiring treatment.

2. Abnormal ABR

The abnormality for an ABR study was: Latencies of wave I, III or V or III-V interval longer than the 90th percentile referenced to laboratory-established norms for GA; absence of detectable component or components (Karmel et al., 1988, 1998).

B. Exclusion criteria

Newborns with congenital or chromosomal defects, known prenatal exposure to drugs of abuse, known HIV exposure and infants who failed OAE testing were excluded.

C. Informed consents

Informed consents were obtained from parents of all infants as part of a research project to study arousal and attention of NICU infants conducted by New York State Institute for Basic Research (IBR) personnel under NICHD R01-HD21784 grant to Dr. Judith M. Gardner and NIDA R01-DA006644 grant to Dr. Bernard Z. Karmel. All experimental protocols were reviewed and approved by the Integrated Scientific and Ethical Review Board St. Vincent's Catholic Medical Centers, Manhattan, RUMC, and Institutional Review Boards of IBR and the City University of New York (CUNY)/College of Staten Island.

II. Stimulus generation

A. ABR study

Stimuli consisted of 100 μsec rectangular rarefaction clicks presented at a rate of 12.9/second and were generated using Intelligent Hearing System, Inc. Smart EP Program (Intelligent Hearing System, Inc., Miami, FL, USA). Stimuli were delivered to the baby's left ear through an Etymotic Research, ER-3A tube-earphone coupled system. Left side ears were considered the standard side to test in our study because they were more accessible at the bedside

due to infants' favor of turning their heads toward the right (Gardner et al., 1977). Moreover, ABR responses in newborn infants tend to be similar for both ears (Karmel et al., 1988).

B. FFR study

A complex tone was generated using SIGNAL digital signal analysis language (Engineering Design, Berkeley, CA, USA) (Patel & Balaban, 2001). The tonal complex consists of 3 frequency components (F1, F2, F3) of 650, 950 and 1250 Hz in cosine phase with duration of 500ms. A long tone stimulus (500ms) has been shown to enhance amplitude of auditory steady state evoked potential to the missing fundamental (MF) complexes (Lutkenhoner, Lammertmann & Knecht, 2001; Winkler, Tervaniemi & Naatanen, 1996). On the other hand, using a short tone stimulus (50ms) Chambers, Feth & Burns (1985) failed to find the existence of MF in FFR spectra content. Stimuli were delivered to the baby's left ear through the same Etymotic Research ER-3A tube-earphone coupled system. Tube-earphone coupling minimized electromagnetic contamination of the FFR.

III. Data collection procedure

ABR and FFR were studied as early as possible after birth, starting from the 2nd day of life but no earlier than 32 weeks PCA. Based on observations with previous ABR studies, twenty-four hours were considered needed to clear after a birth any remaining vernix caseosa, a greasy, wax-like substance from the ear canal. On the other hand, testing before 32 weeks PCA was susceptible to collapsed or too restrictive auditory canals that could result in not having an clear air passage to the ear drum. These conditions would result in intensity-compromised waveforms and be inappropriately identified with component latency delays.

A. ABR study

ABRs were recorded differentially between scalp electrodes placed on the vertex and left mastoid. An electrode on the midline of the forehead served as the ground. All electrode impedances were below 7 kΩ. EEG inputs were amplified by 200,000 and bandpass ~ 3dB filtered from 150-3000 Hz. The recording time window was 12 msec. Each response waveform represented an average of 2x1024 (2048) stimulus presentations. Any signal above 12.5 μV was considered artifacts and automatically rejected from the recorded responses. Sound level of the stimulus was calibrated to approximate 75 dB using a Bruel and Kjaer sound level meter coupled to a standard Bruel and Kjaer artificial ear. Stimulus delivery, artifact rejection, and response averaging were carried out using an Intelligent Hearing System Smart EP hardware and software module on an IBM-compatible computer.

B. FFR study

The electrode recording sites were the same as those used for ABR. Stimuli with condensation and rarefaction polarities were presented alternatively within one trial. EEG inputs were amplified by 100,000 and bandpass filtered from 100-3000 Hz. Each response waveform represented an average of 2048 stimulus presentations. Responses above 8 μV were considered artifacts and automatically rejected from the averaged responses. Sound level of the stimulus was calibrated to approximate 75 dB using a Bruel and Kjaer sound level meter coupled to an standard artificial ear. Stimulus delivery and response averaging were similarly carried out using an Intelligent Hearing System, Inc. Steady-State hardware and software module running on an IBM-compatible computer. Electrode impedance was less than 7kΩ for all recordings.

C. CUS information

CUS information, when a CUS was performed, was obtained from the clinical record. The most severe pathology noted over serial testing was used to classify infants independent of the age of the infant when tested. Other available clinical information, i.e, CT, MRI, also was used to help determine BI and severity of BI.

D. OAE

Information from transient evoked OAE routinely obtained under clinical protocols at hospital discharge was extracted from the clinical record to provide an indication of auditory periphery integrity. All study infants passed the hospital's OAE hearing screenings.

IV. Data analysis

A. ABR study

Component latencies (CLs) and interpeak latencies (IPLs) were computed on-line and measured in msec. CLs were labeled as I-VII consecutively, with special emphasis on I, III and V CLs and III-V IPLs. Delays in any CLs and prolonged IPLs greater than the 90^{th} percentile compared to our laboratory-constructed norms were considered abnormal ABRs. All ABRs measurements and decisions were reviewed for accuracy by BZ Karmel.

B. FFR study

FFR recordings were analyzed off-line. First the output files were converted into Microsoft Excel spreadsheets using a dedicated program. The sum and difference of the two conditions were obtained. Each condition contained the equal number of points. These addition and subtraction manipulations were used to enhance the component of the FFR phase-locked to the envelope-related frequency and stimulus component frequencies, respectively (Greenberg,

1987; Richman et al, 1991; Wile & Balaban, 2007). Figure 1 summarizes the process to obtain the sum and difference waveforms (adapted from Wile and Balaban, 2007). The complex signal consisting of the two stimulus conditions is depicted in the upper right-hand corner of the graph.

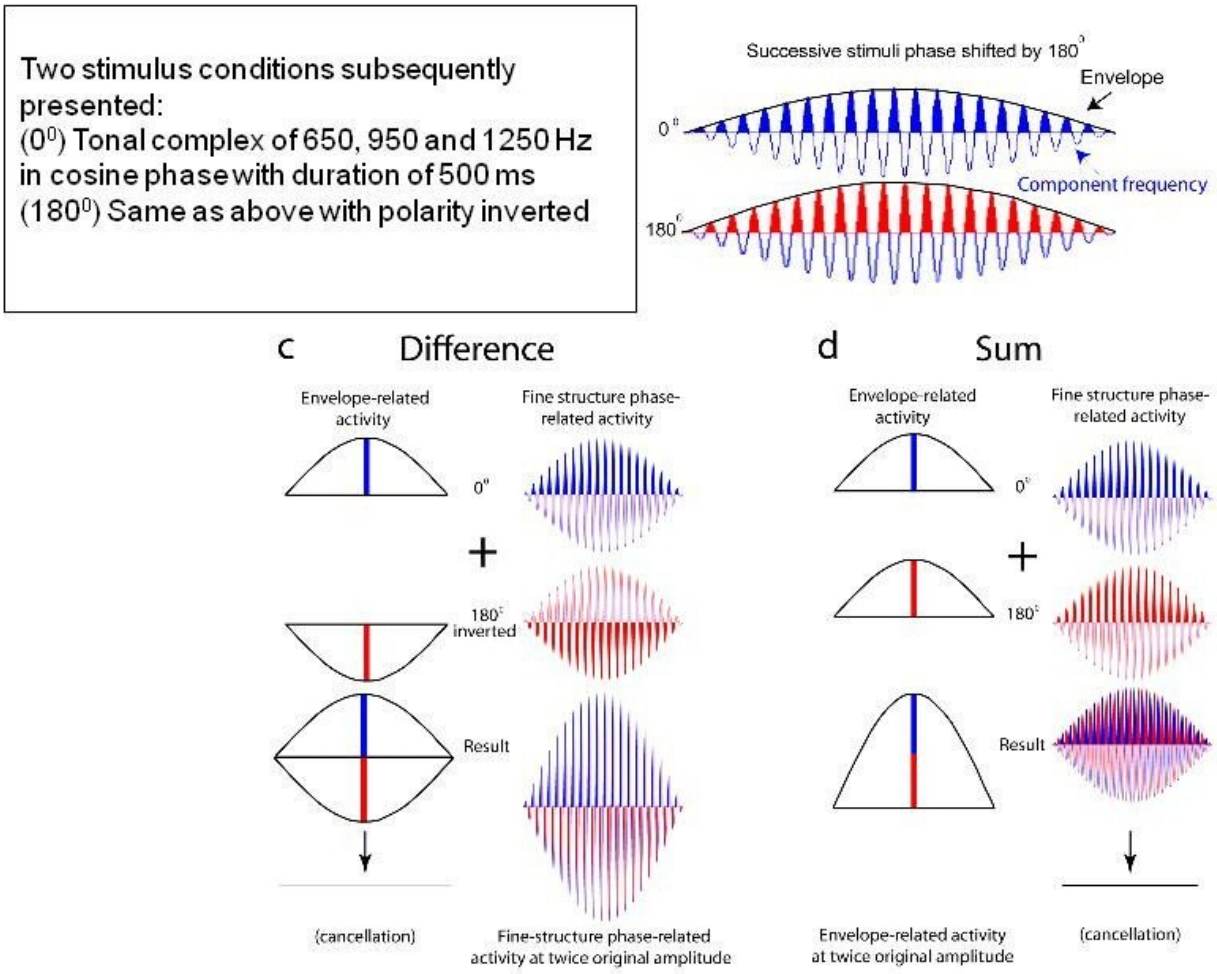

Figure 1. Difference waveform generated by multiplying the 180° response waveform by −1 and adding it to the 0° response waveform. Sum waveform generated by adding the 0° response waveform to the 180° response waveform. A more detailed description can be obtained through the internet linkage below:

(http://www.plosone.org/article/info:doi/10.1371/journal.pone.0000369#references)

Fast-Fourier transformation (FFT) on the first 4096 data points of the FFR sum and difference were obtained using Microsoft Excel® Analysis ToolPak, an add-on data analysis function. The FFT spectra of the sum and difference were displayed using SYSTAT® Table 2D v.5.01 software program (SYSTAT® Software, www.systat.com) (see Figures 2, 3). Figure 2 depicts an exemplar of the sum waveform. It showed the responses to the envelope-related (ER) frequency f2-f1 (f300) and its harmonic frequencies (i.e, f600, f900, f1200). Figure 3 displays a difference waveform with responses to the fine-structure related frequencies. There are two types of fine structures: distortion product (DP)-related 2f1-f2 (f350) and stimulus component-related (f650, f950, f1250).

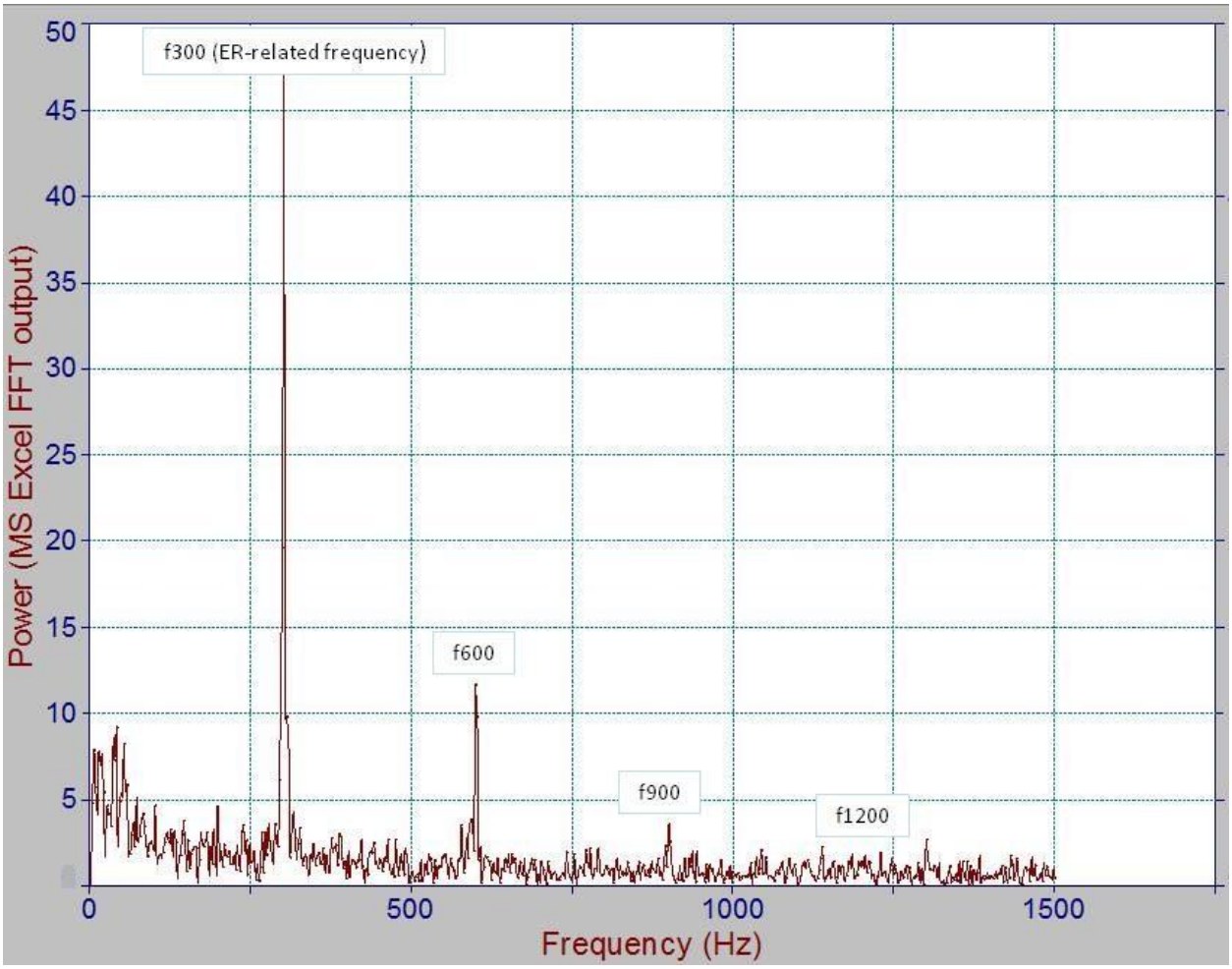

Figure 2. Exemplar of the sum spectra displayed using Table Curve 2D. Envelope-related (ER) response in the recorded FFR spectrum or f300 and its harmornics (i.e, f600, f900, f1200) are shown in the power spectra.

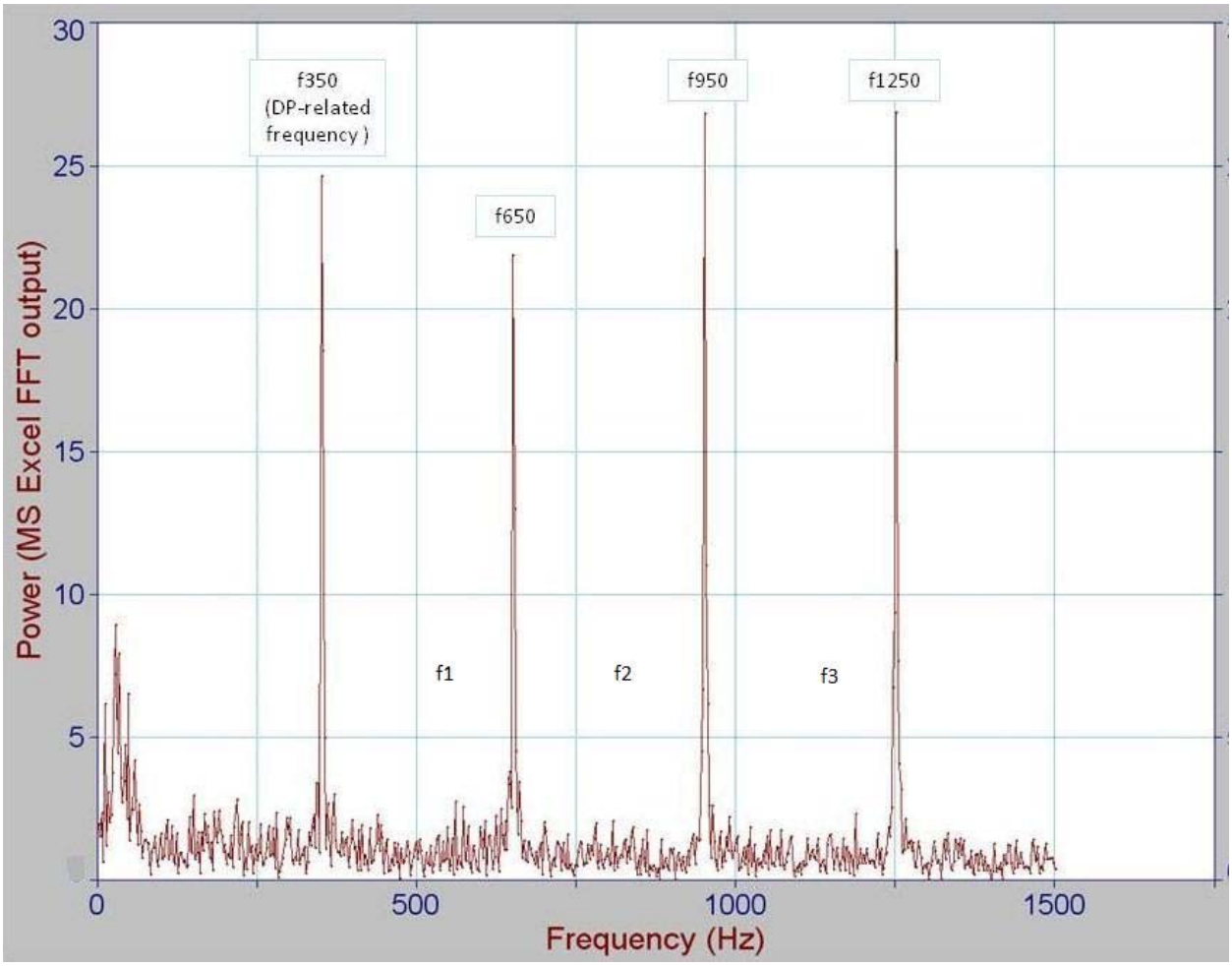

Figure 3. Exemplar of the difference spectra displayed using Table Curve 2D. There are 2 types of fine structure-related responses: distortion product (DP) related response at a frequency of 2f1-f2 (i.e, f350) and component frequencies (CFs) responses at stimulus-related frequencies (f1, f2, f3 or f650, f950, f1250).

To assess the relative strength of the FFR at a specific frequency, the FFT power outputs of each individual data were normalized. A z-score for each frequency then was obtained. It should be noted that the average z-score across the spectral power for each case would be 0.0 with SD = 1.0 by definition. Statistical treatment of the data to select peaks used paired t-tests to

examine the significant differences between mean responses of targeted frequencies and those of nearby frequencies within +/-8Hz. A response was considered physiological relevant when its a z-score ≥ 2. To test the main effect of age and brain injury General Linear Models (GLM) was used with the z-scores of spectral energy as the dependent variable and group as the independent variable. $\alpha = 0.05$ was used to determine statistical significance.

Hypothesis #1: Processing of complex tones emerges during the perinatal period

To test this hypothesis, we studied the development of FFR to targeted frequencies by examining the main effect of age on the relative strength of responses at component-related, DP-related, and ER-related frequencies. We also tested for the presence of physiological relevant response at the targeted frequencies.

Hypothesis #2: Pitch-related information processing relies on the integrity of the auditory pathway.

To test this hypothesis, we examined the FFR results from brain injured (BI) and non-BI (normal) newborns. We determined whether the pitch-related information processing is interfered by injury to areas involved in the processing of auditory stimuli, as indicated structurally by abnormal CUS and/or as functionally by abnormal ABR. Relative strength at targeted frequencies (component-related, DP-related and ER-related frequencies) were examined in BI and non-BI groups.

CHAPTER 3- RESULTS

I. Study population characteristics

A total of 128 infants born at Richmond University Medical Center (RUMC) in Staten Island, formerly known as St. Vincent's Catholic Medical Center (SVCMC)-Staten Island, were studied cross-sectionally during the perinatal period (55% were boys). Mean gestational age (GA) at birth was 34 weeks (range 23-41 weeks). Postconceptional age (in weeks) at test (PCA) (calculated as the GA + (# days after birth/ 7)) was 36 weeks +/-2.51 weeks, (range 32-46 weeks) (see table 1). There were 3 CNS injury study groups: 1) normal (with normal ABR and CUS) (n=58); 2) abnormal ABR only (Abn-ABR) (n=60); and, 3) abnormal CUS group (Abn-CUS) (n=10). There were no significant differences in gender ($\chi^2_{(df=2)} = 4.46$, $p < 0.11$) among these 3 groups (see Table 2 and Figure 4)**.** Table 2 provides the N and percents while the bar graph in Figure 4 displays the frequencies of males and females in the 3 groups. However, age at test was significantly different between groups ($F_{(2,125)} = 15.11$, $p < 0.001$). Infants in the Abn-CUS group were significantly older at the time of test (see Figure 5 and, 6). The bar graph in Figure 5 summarizes age at test and distribution of gender in the 3 study groups. Figure 6 collapsed across gender and depicts the significant older age at test of the Abn-CUS group.

Table 1. Descriptive statistics of the study population

	N	Minimum	Maximum	Mean	Std. Deviation
EGA (weeks)	128	23	41	34	3.60
BW (grams)	128	595	4196	2108.52	814.54
Age at test (wks)	128	32	46	36	2.51
APGAR at 5 min	128	0	9	7	2
APGAR at 10 min	128	1	9	8	1

Table 2. Distribution of gender among the 3 study groups

	Normal (ABR&CUS)	Abnormal ABR only	Abnormal CUS	Total
Males	27 (38.6%)	35 (50%)	8 (11.4%)	70 (100%)
Females	31 (53.5%)	25 (43.1%)	2 (3.4 %)	58 (100%)
Total	58 (45.3%)	60 (46.9%)	10 (7.8%)	128 (100%)

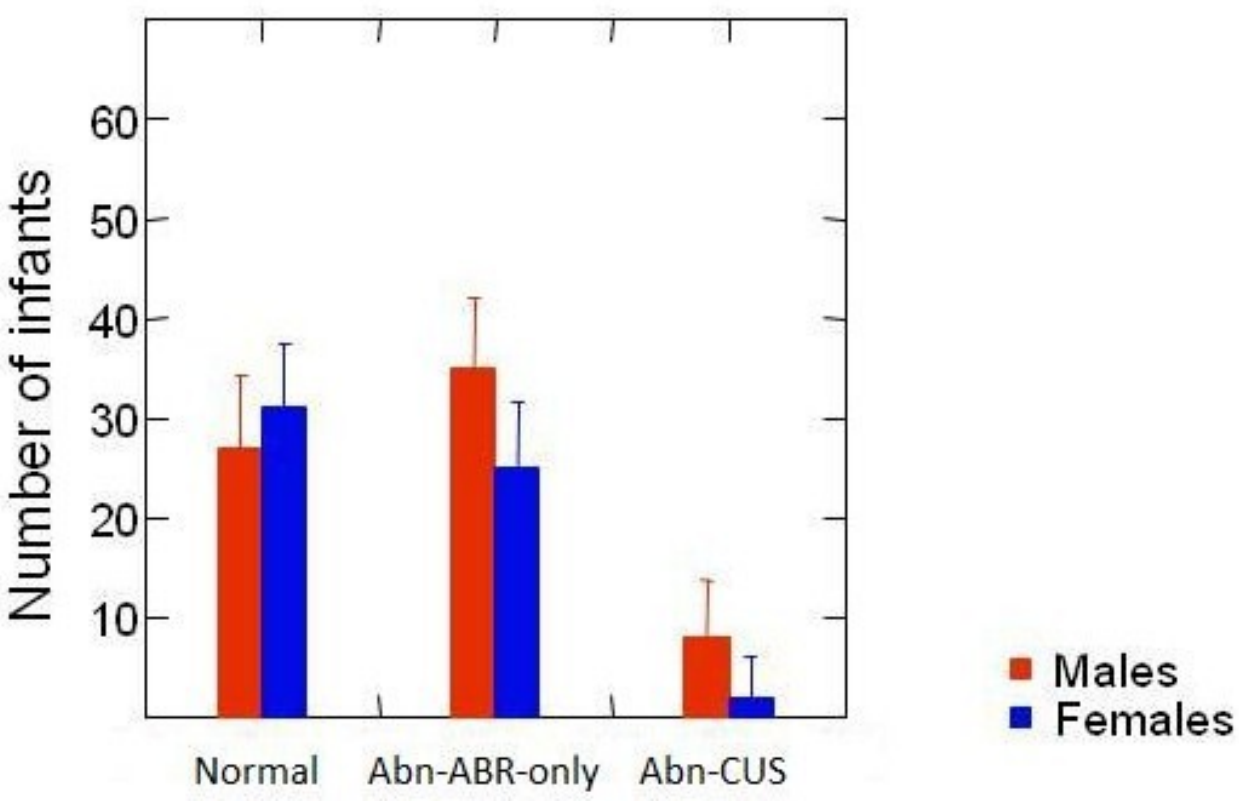

Figure 4. Distribution of gender among 3 study groups. Error bars represent standard error of the mean.

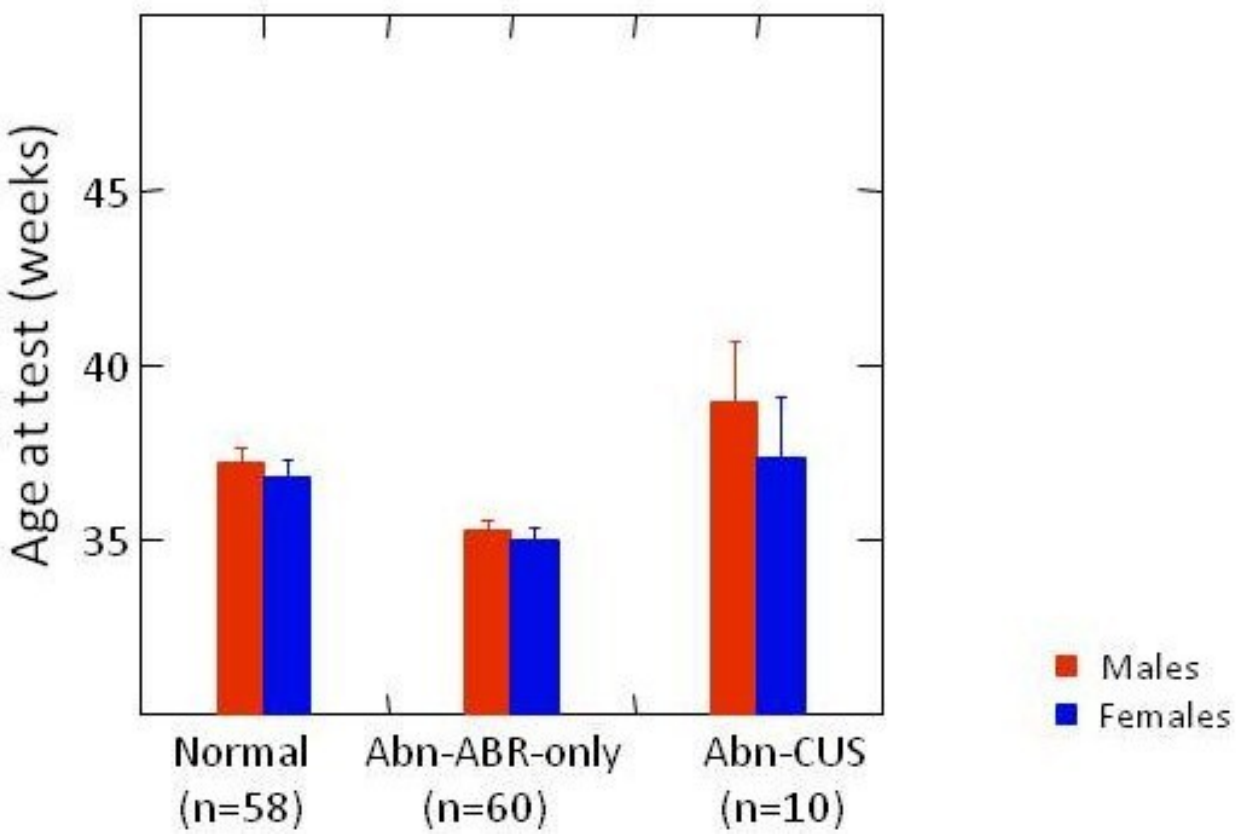

Figure 5. Distribution of age at test and gender among 3 study groups: normal, abnormal ABR only and abnormal CUS. Error bars represent standard error of the mean.

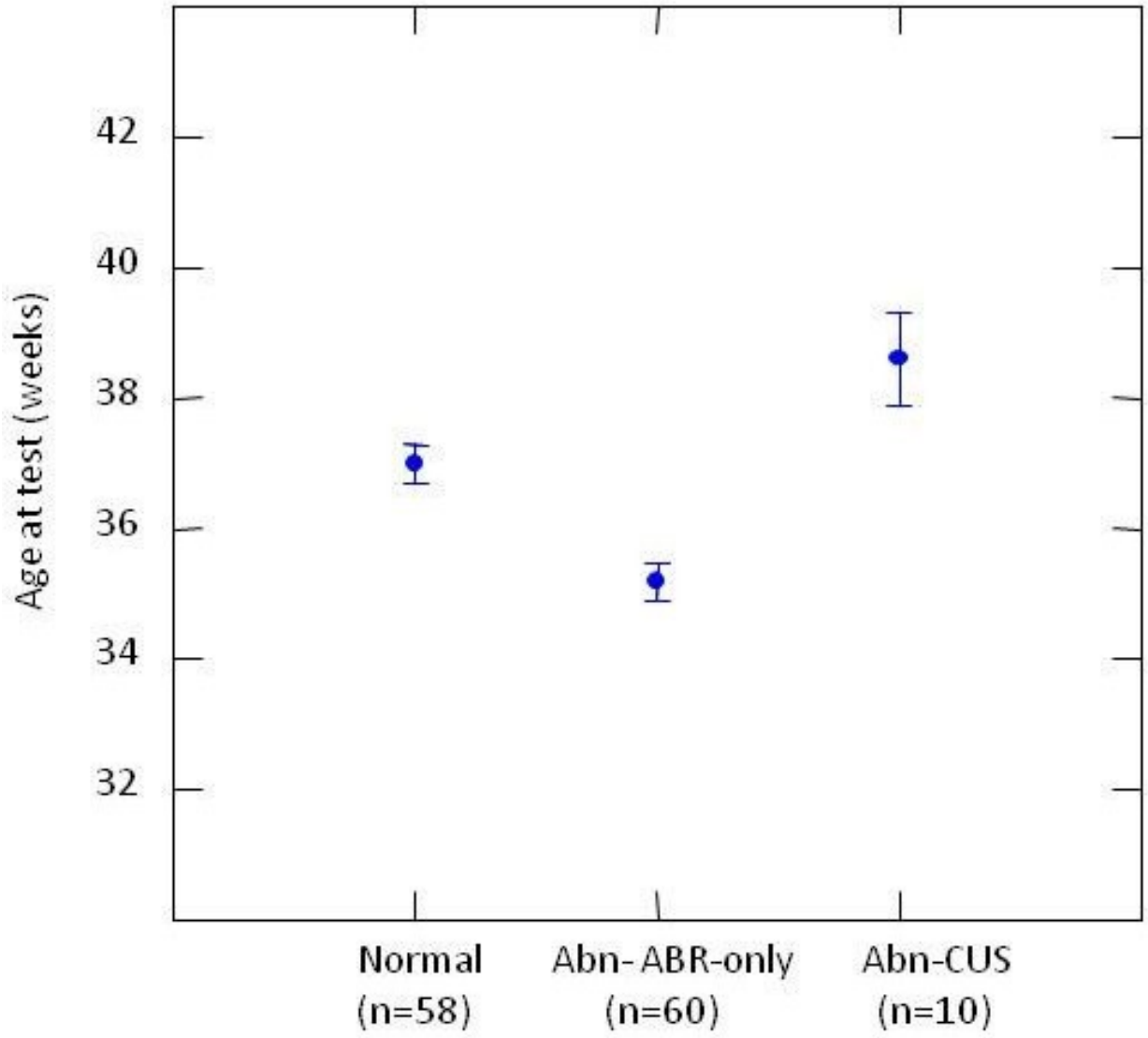

Figure 6. Significant increase in age at test of the abnormal-CUS group. Error bars represent standard error of the mean.

I. FFR development over age

A. Peak selection

1. *Analysis of the sum spectra*

Peak selection: The magnitude of the spectral energy near the targeted frequencies (fs), ER frequencies (f2-f1, i.e. f300) and its harmonics, i.e. f600, f900, f1200 were tested

for significant differences to their neighbor fs within ±8Hz using paired t-tests. We used 8Hz due to the fact that FFT is operated in the power of 2 data points (e.g., $8 = 2^3$). Distribution of the responses near the targeted fs in the sum spectra across subjects was shown in Figures 7, 8, 9, 10 and Table 3. 96% of the infants had responses to frequency near f300 of $z \geq 2$ (peak-relevant) (see figure 7). However, responses to frequency near f600 reach peak-relevant in only 26% of infants (see figure 8). Furthermore, responses near f900 and f1200 gave $z<1$ in almost all cases (see figure 9, 10 and table 3). The histogram in Figure 9 displays the distribution of responses near f900 while responses near f1200 are shown in Figure 10. Table 3 summarizes descriptive statistics of responses to ER-related f300 and its harmonics f600, f900, f1200 in the sum spectra. Because responses to f900 and f1200 in all infants were not peak-relevant (z-scores <2) no further examinations on these fs were performed.

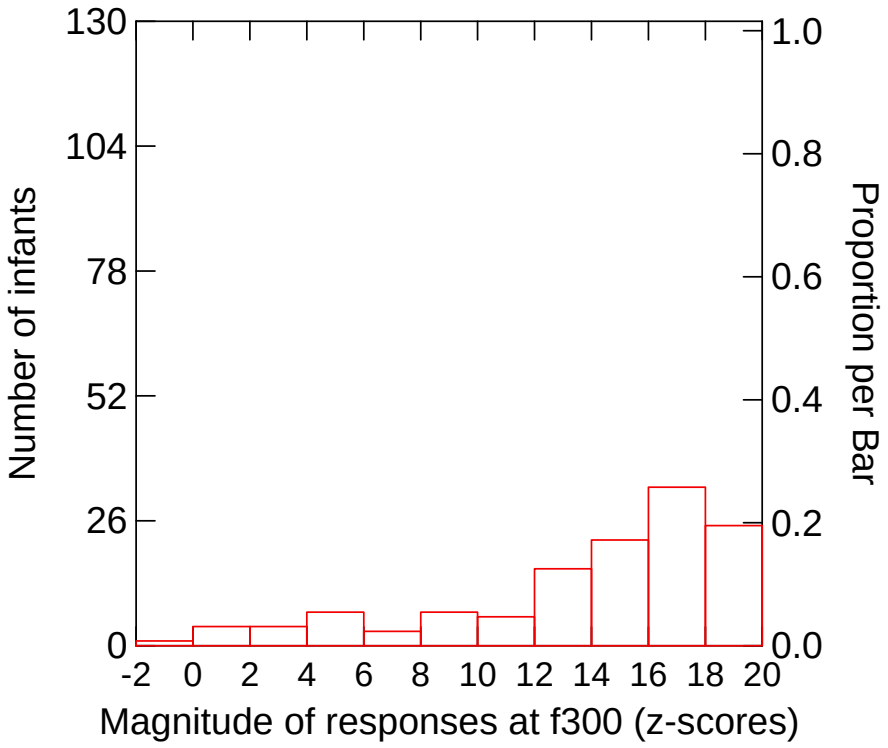

Figure 7. Distribution of responses at f300

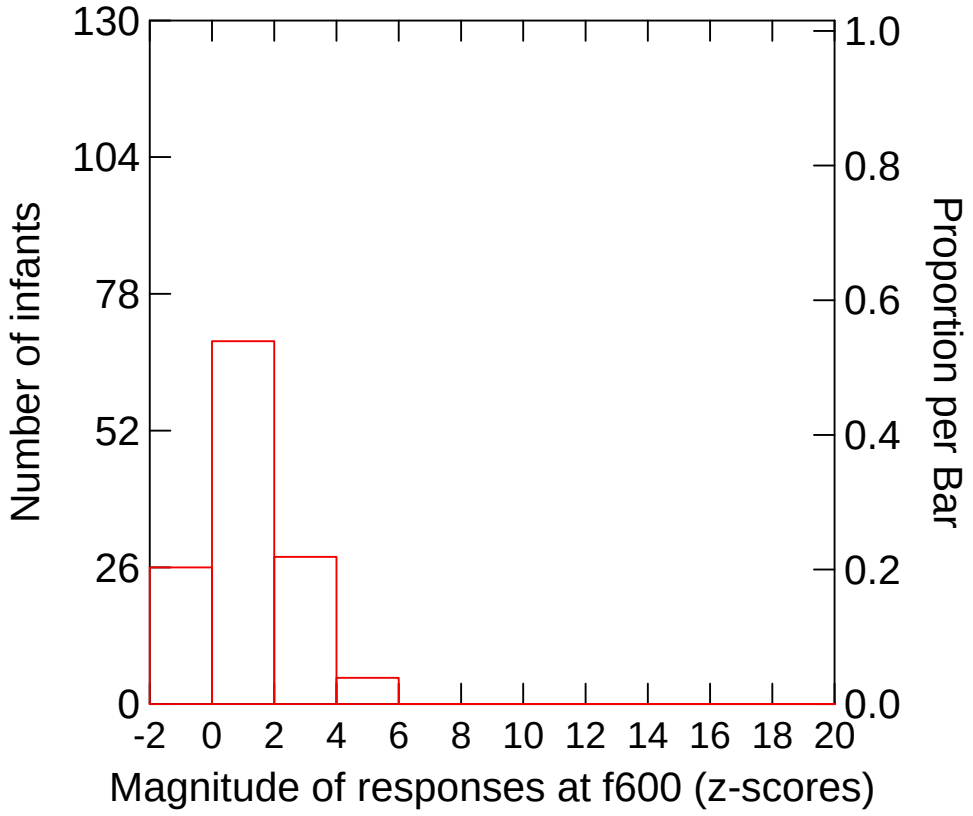

Figure 8. Distribution of responses at f600

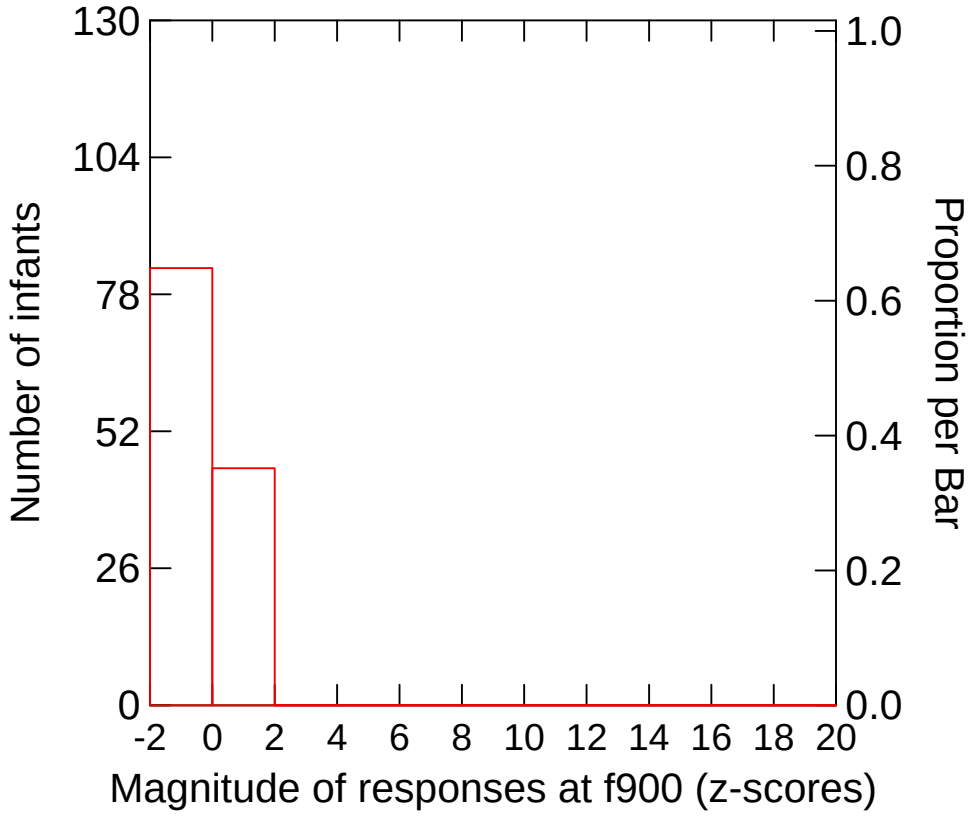

Figure 9. Distribution of responses at f900

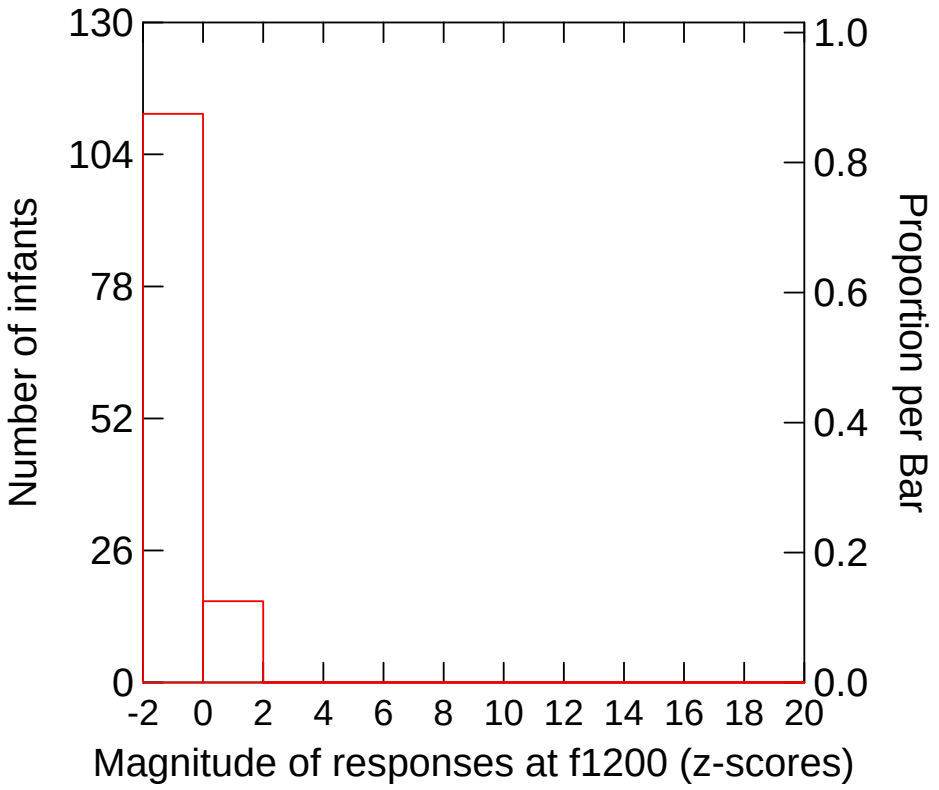

Figure 10. Distribution of responses at f1200

Table 3. Descriptive statistics of responses at frequencies at f300, f600, f900 and f1200

Frequencies	N	Min.	Max.	Mean	Std.Dev.	Skewness	Kurtosis
f300	128	-.79	19.47	13.74	4.99	-1.19	.49
f600	128	-1.15	5.22	1.17	1.29	.65	.15
f900	128	-1.05	1.23	-.10	.46	.66	.54
f1200	128	-1.54	.97	-.34	.37	.13	1.96

a. Peak near the envelope-related frequency f300

When responses to f300 were compared to those of the neighboring fs we found that f300 mean of responses was higher (see Figure 11) as well as significantly different to them (paired t-tests, all p's < 0.001, see Appendix 1). Additionally, when the differences in means of these pairs were examined they were in the magnitude of $z \geq 7$ (see Appendix 2). Figure 11 depicts the mean of responses to f300 (normalized power) as well as to its neighbors of ±8Hz.

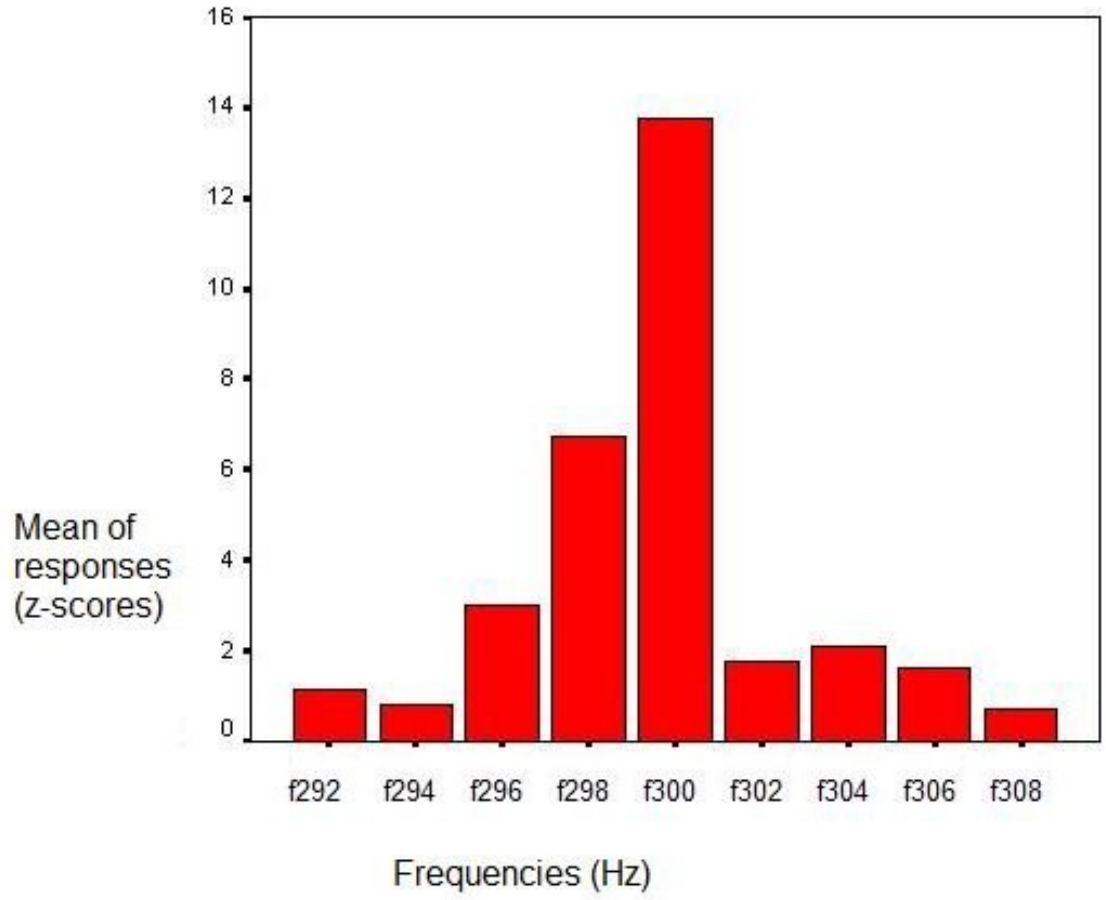

Figure 11. Histogram of mean responses at f300 and neighboring frequencies (f292 ... f308). Notice a higher mean of responses at f300.

b. Peak near the envelope-related harmonic frequency f600

When responses to f600 and to those of neighboring fs were compared, we found that the mean of responses with f600 was higher as well as significantly different (paired t-tests, all $p<0.001$, see Appendix 3). Figure 12 displays the mean of responses to f600 as well as to its neighbors of ±8Hz. Unlike the responses to f300, f600 mean of normalized power were < 1.5. On the other hand, when paired differences were examined, they were still within the noise level ($z\geq0.9$) (see Appendix 4). Pair f600-f598 was far below in level due to the fact that their powers of responses were similar (see Figure 12). In summary, only the responses to f300 and its harmonic f600 in the sum spectra proclaimed significant effects.

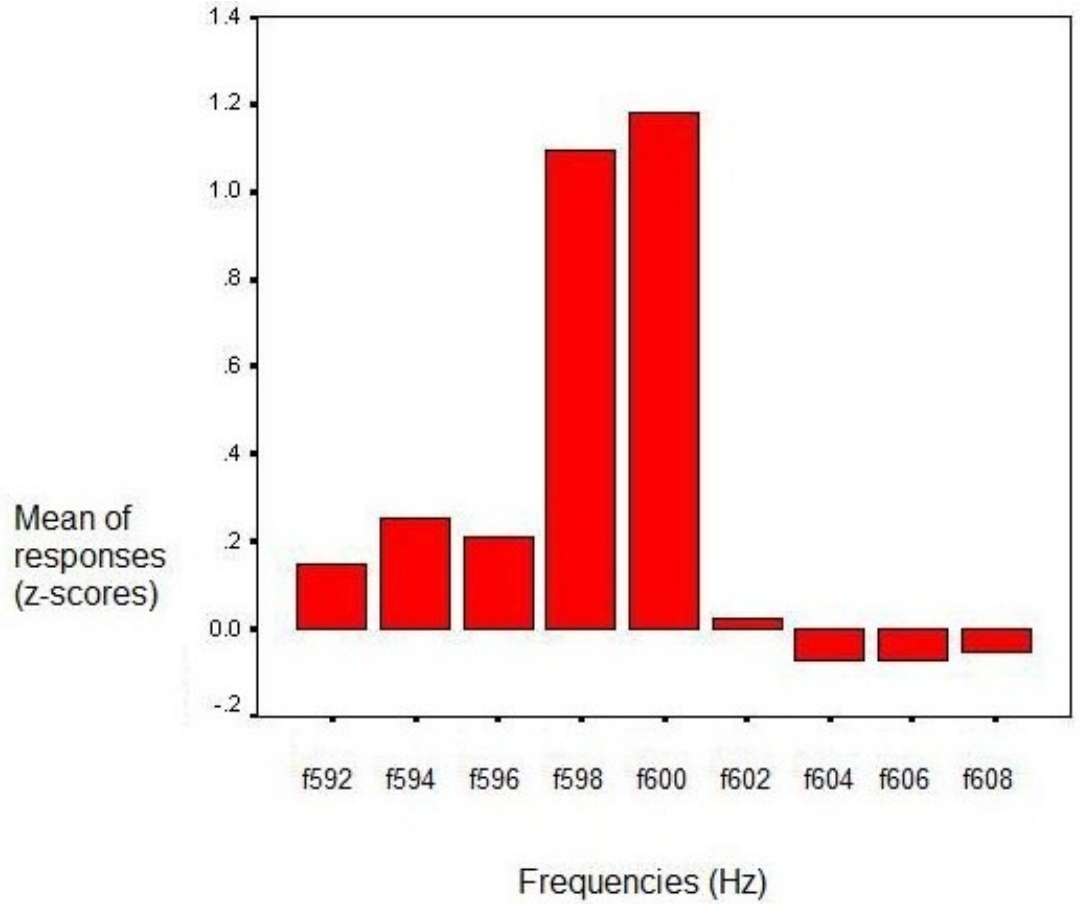

Figure 12 . Histogram of mean responses at f600 and neighboring frequencies (f592…f608). Notice a higher mean responses at f600.

2. Analysis of the difference spectra

Peak selection: Spectra energy near the component frequencies f650, f950, f1250, DP-related 2f1-f2 (f350) in the difference spectra were tested for significant differences to their neighbor fs within ± 8Hz using paired t-tests. Distribution of the responses near the targeted fs in the difference spectra was shown in figures 13, 14, 15, 16 and table 4. More than 70% of the infants had responses to all targeted frequencies of $z \geq 2$ (peak-relevant). Responses to f350, shown in Figure 13, reached peak-relevant in N=92 infants. Similarly, normalized power of

responses z ≥ 2 to f650 (Figure 14), f950 (Figure 15), f1250 (Figure 16) were found in N=96, 112 and 101 infants, respectively. Statistical summary of these responses was shown in table 4.

Table 4. Descriptive statistics of responses at frequencies f350, f650, f950 and f1250

Frequencies	N	Minimum	Maximum	Mean	Std. Dev.	Skewness	Kurtosis
f350	128	-.45	17.01	4.33	3.93	1.14	.96
f650	128	-1.14	14.94	6.21	4.36	.34	-1.15
f950	128	-1.37	17.53	7.36	4.63	.02	-1.12
f1250	128	-.62	13.34	4.82	3.35	.28	-.79

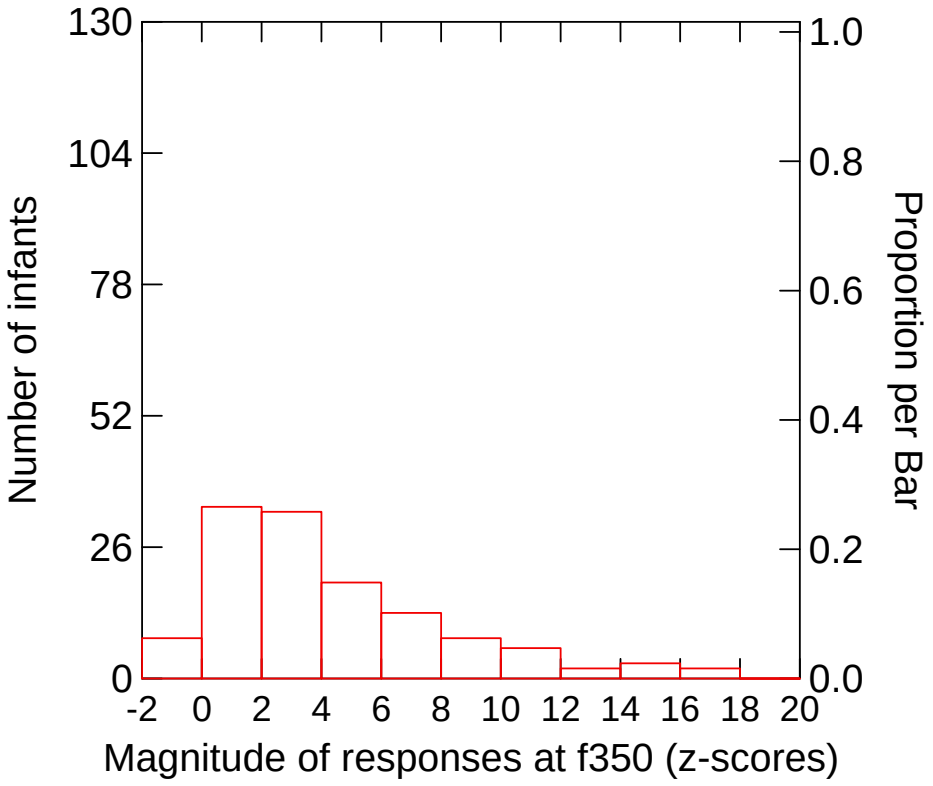

Figure 13. Distribution of responses at f350

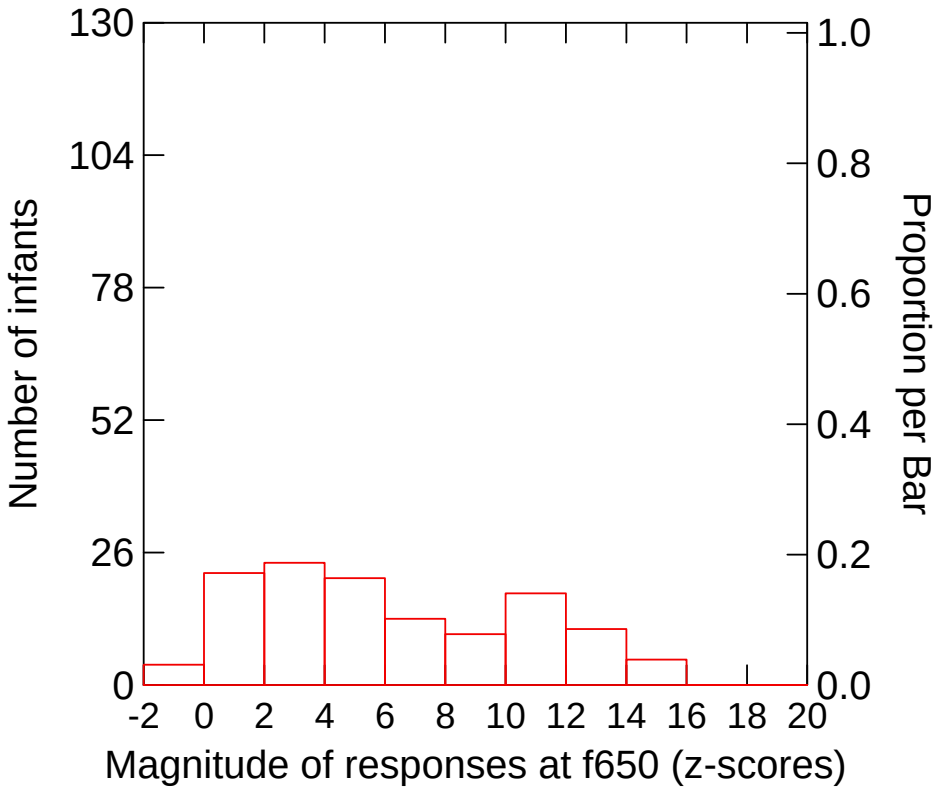

Figure 14. Distribution of responses at f650

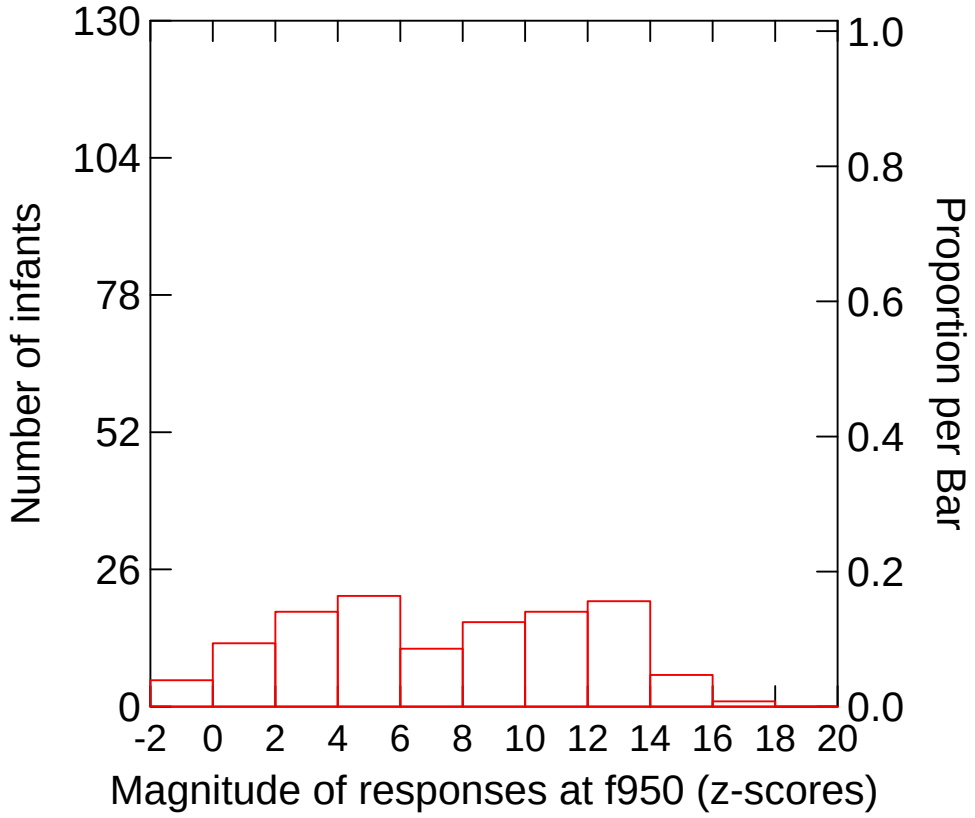

Figure 15. Distribution of responses at f950

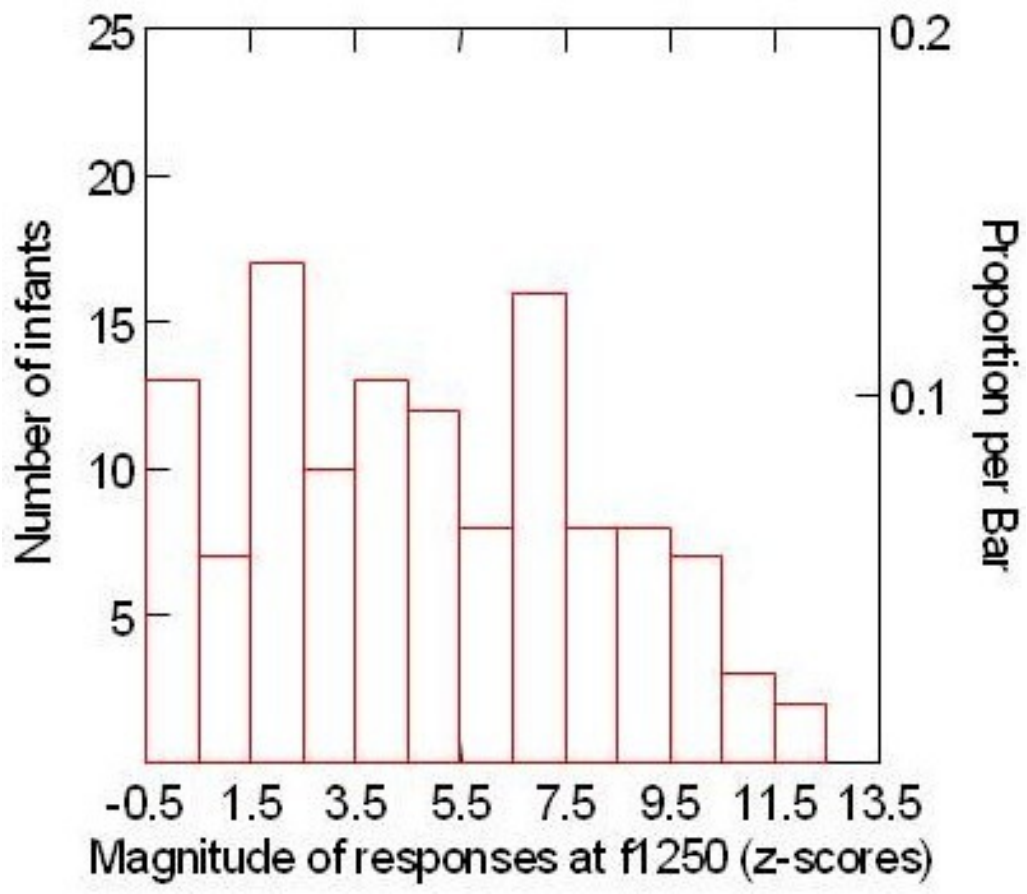

Figure 16. Distribution of responses at f1250

a. Peak near the DP-related frequency f350

When responses to f350 to those of the neighboring fs were studied, we found that f350 mean response was higher. The normalized power in these examined frequencies is displayed in Figure 17. Additionally, paired t-tests comparing f350 and neighboring frequencies (f342 … f358) showed statistical significantly differences (all $p < 0.001$, see Appendix 5). Likewise when the means of paired differences were examined, they were in the magnitude of z>/=1.6 (see Appendix 6).

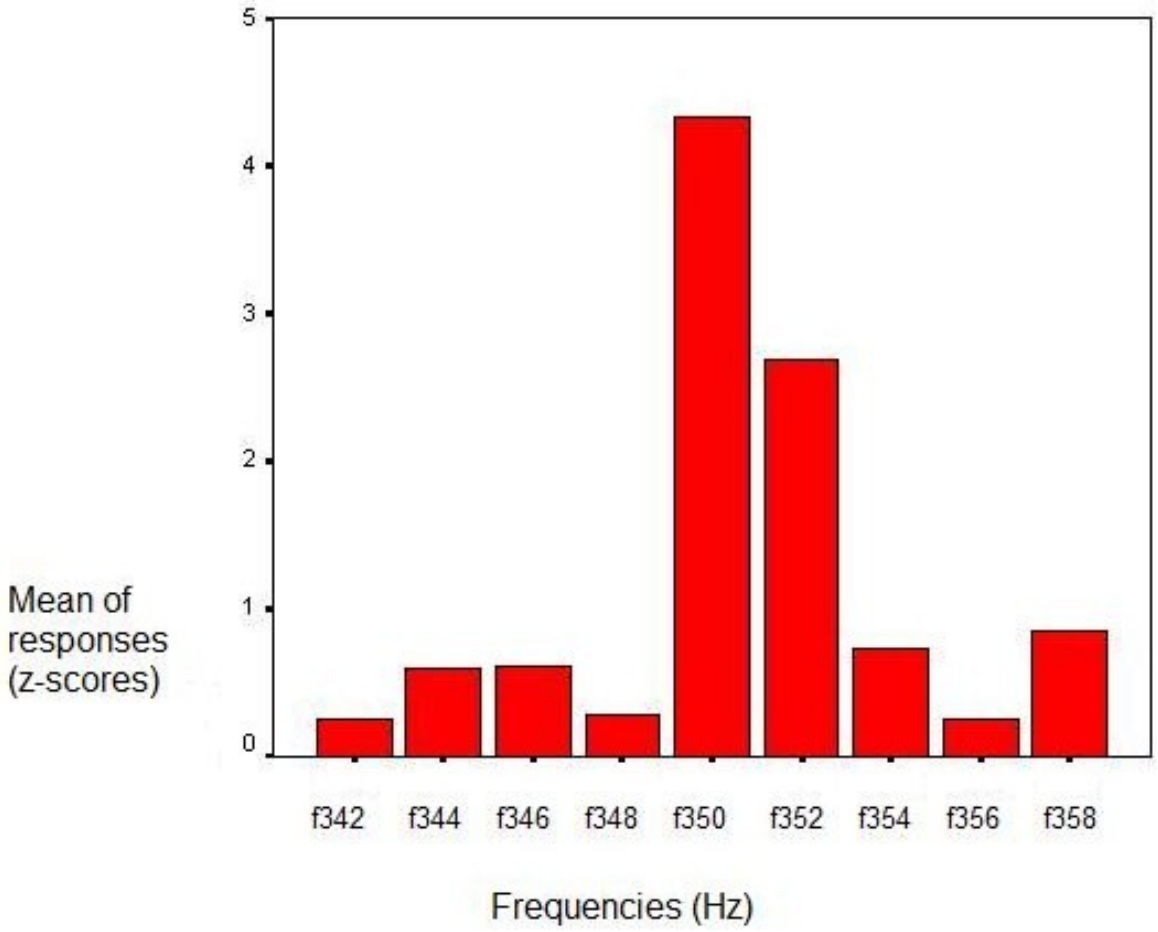

Figure 17. Histogram of mean responses at f350 and neighboring frequencies (f342 … f358). Notice a higher mean responses at f350.

b. Peak near the envelope-related frequency f650

When responses to f650 to those of the neighboring fs were compared, we found that, as with f350, the f650's mean of responses was significantly more powerful. The normalized power in these examined frequencies is shown in Figure 18. Furthermore, all paired t-tests comparing f650 and neighboring frequencies (f642 … f648) reached statistical significantly differences (all $p<0.001$) (see Appendix 7). Likewise when the means of paired differences were examined, they were in the magnitude of $z>/=2.9$ (see Appendix 8).

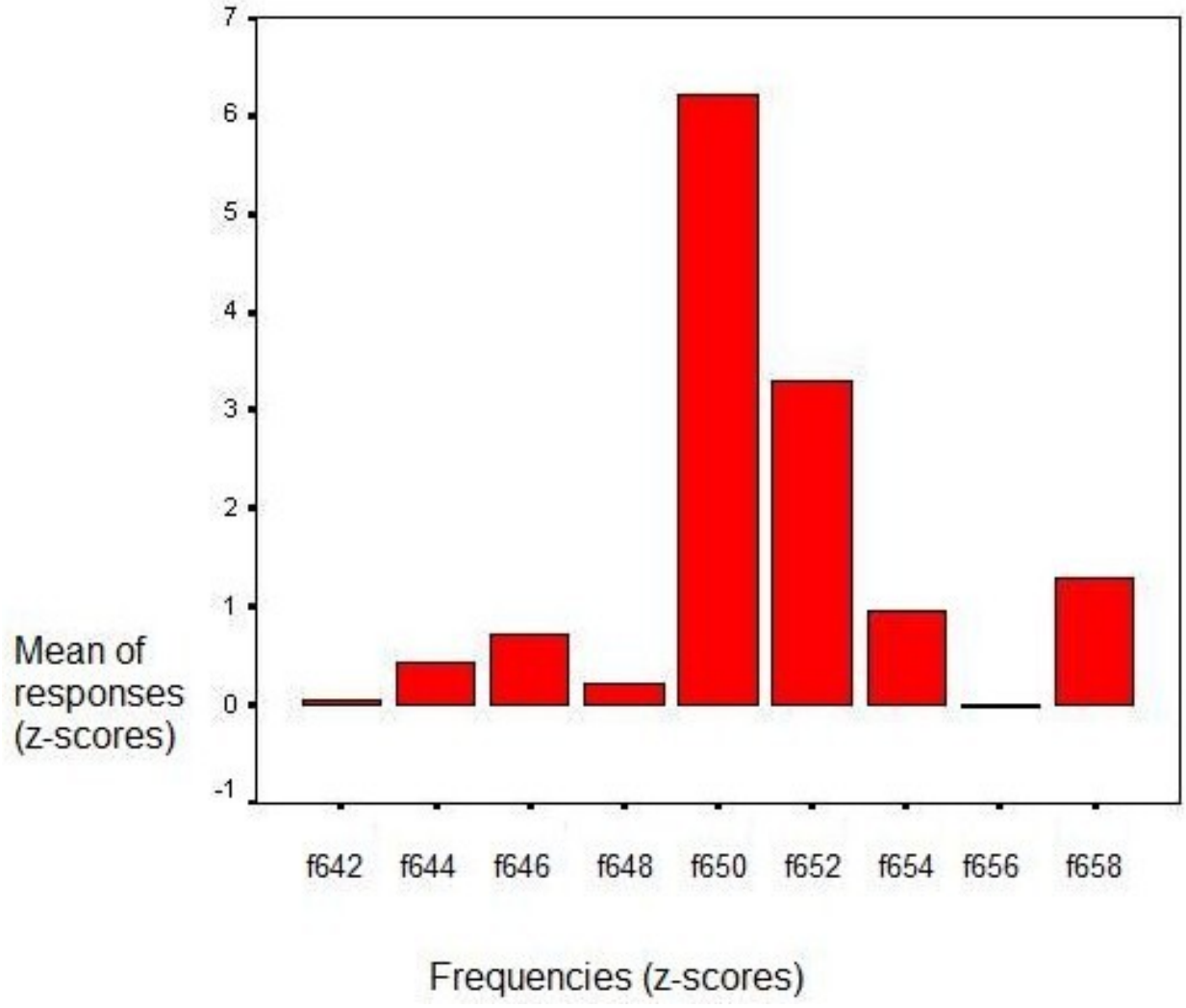

Figure 18 . Histogram of mean responses at f650 and neighboring frequencies (N642 … N658). Notice a higher mean responses at f650.

c. Peak near the envelope-related frequency f950

When responses to f950 to those of the neighboring fs were examined, we found that f650 mean of responses was more prominent. Figure 19 depicts the normalized power in these examined frequencies. In addition, statistical significantly differences in paired t-tests

comparing f950 and neighboring frequencies (f942 … f958) (all $p<0.001$) were noted (see Appendix 9). Similarly, when the means of paired differences were examined, all their normalized power z>/=4.6 (see Appendix 10).

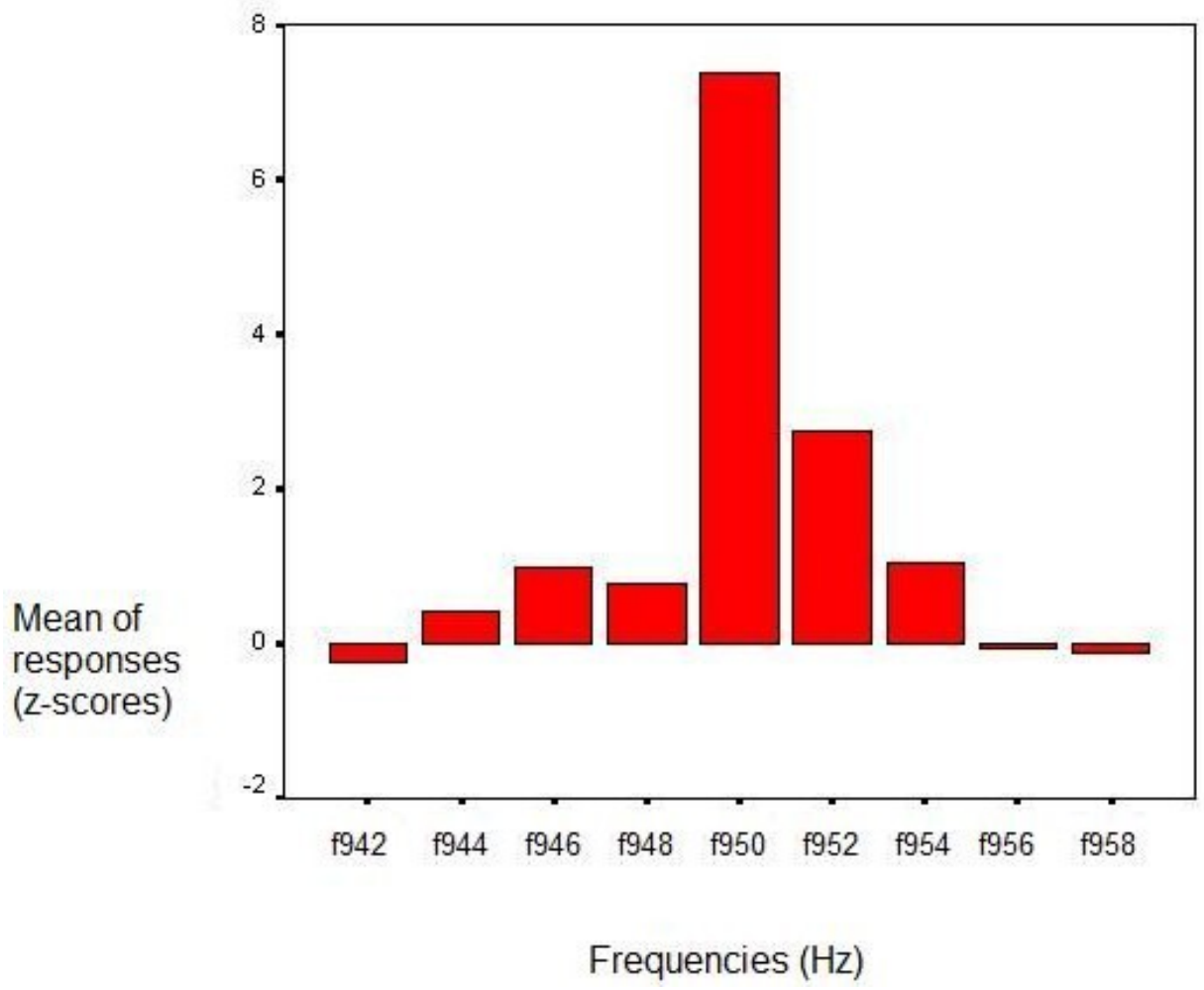

Figure 19. Histogram of mean responses at f950 and neighboring frequencies (f942 … f958). Notice a higher mean responses at f950.

d. Peak near the envelope-related frequency f1250

When responses to f950 to those of the neighboring fs were examined, we found that f650 mean of responses was distinct. The histogram in Figure 20 displays the normalized

power in these examined frequencies, which are statistical significantly differences (paired t-tests comparing f950 and neighboring frequencies (f1242 … f1258), ps<0.001, see Appendix 11). Similarly, when the means of paired differences were examined, all their normalized power were well above the noise floor (z>/=3.8) (see Appendix 12). In summary, all targeted frequencies in the difference spectra (the DP-related frequency f350 and component-related frequencies f650, f950, f1250 were detected.

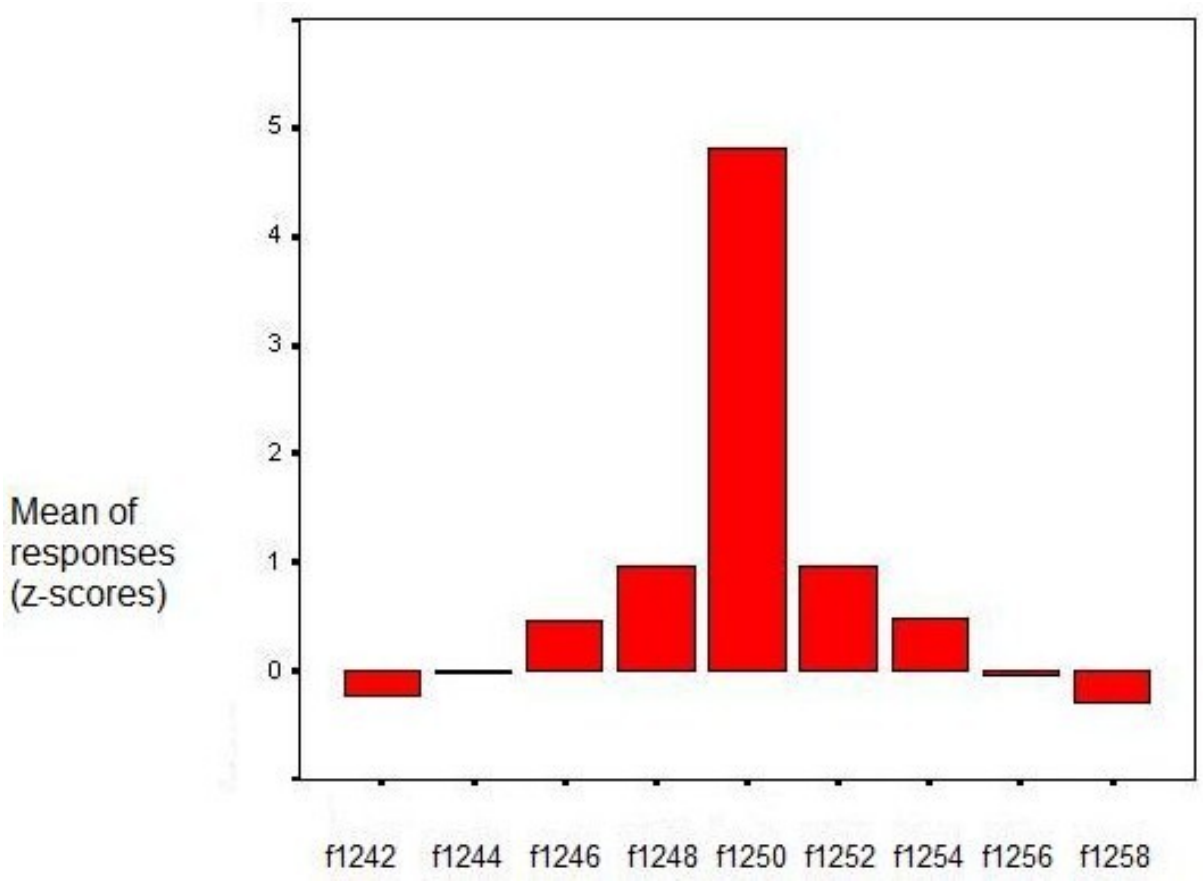

Figure 20. Histogram of mean responses at f1250 and neighboring frequencies (f1242 … f1258). Notice a higher mean responses near f1250.

B. No age effect on the responses to targeted frequencies in sum and difference spectra

When the ages at test were examined we found that they were normally distributed with mean of 36 weeks and standard deviation of 2.5 weeks. The distribution of the ages at test is displayed in a histogram (see Figure 21) as well as summarized in Table 5. In the sum spectra, examination of responses to f300 and f600 showed no significant difference across age at test, even when BI status was taken into consideration. Figure 22 depicts a scatter plot of normalized power at these frequencies over ages with gradient-coded BI status. Similarly, responses at f350, f650, f1250 in the difference spectra were not significantly different across ages (see Figure 23). A summary of the F-tests' statistics is shown in table 6. Although a lower response at f950 was noted at the older age ($p < 0.04$), with Bonferroni-corrected α for $n = 4$ comparisons in the analysis ($\alpha/n = 0.05/4 = 0.01$), it was no longer at reached statistical significance.

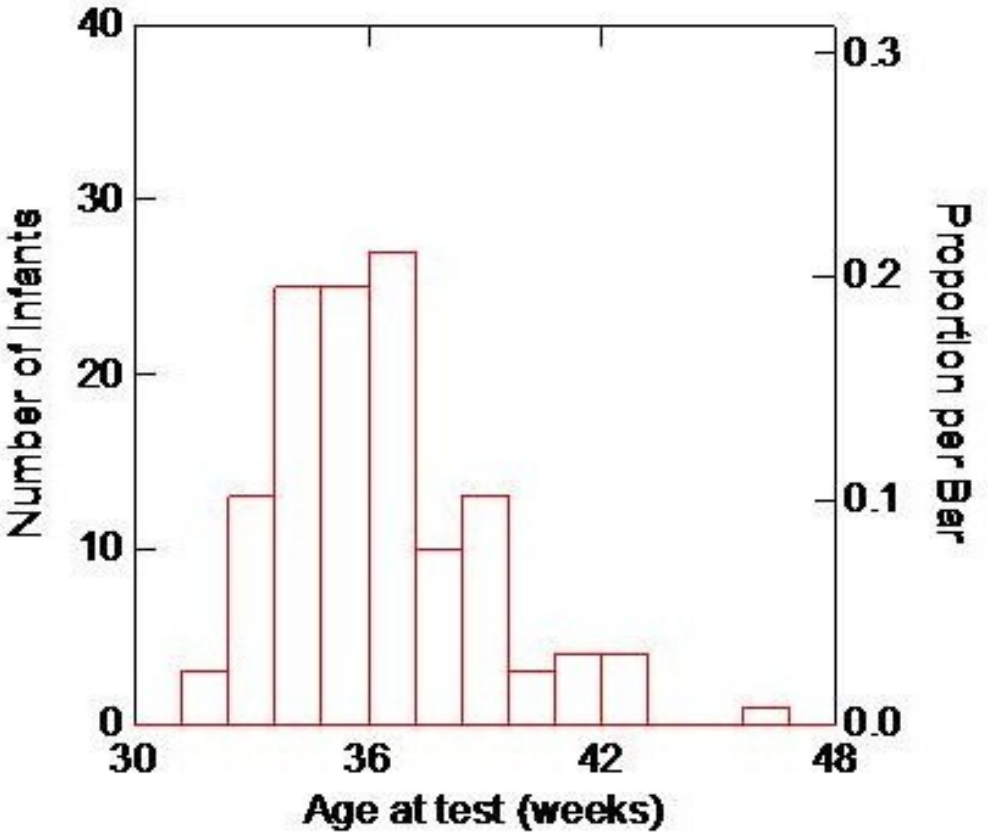

Figure 21. Distribution of age at test.

Table 5. Descriptive statistics of age at test

	N	Min.	Max.	Mean	Std Dev	Skewness	Kurtosis
Age at test (wks)	128	32.14	46.14	36.27	2.51	.99	1.25

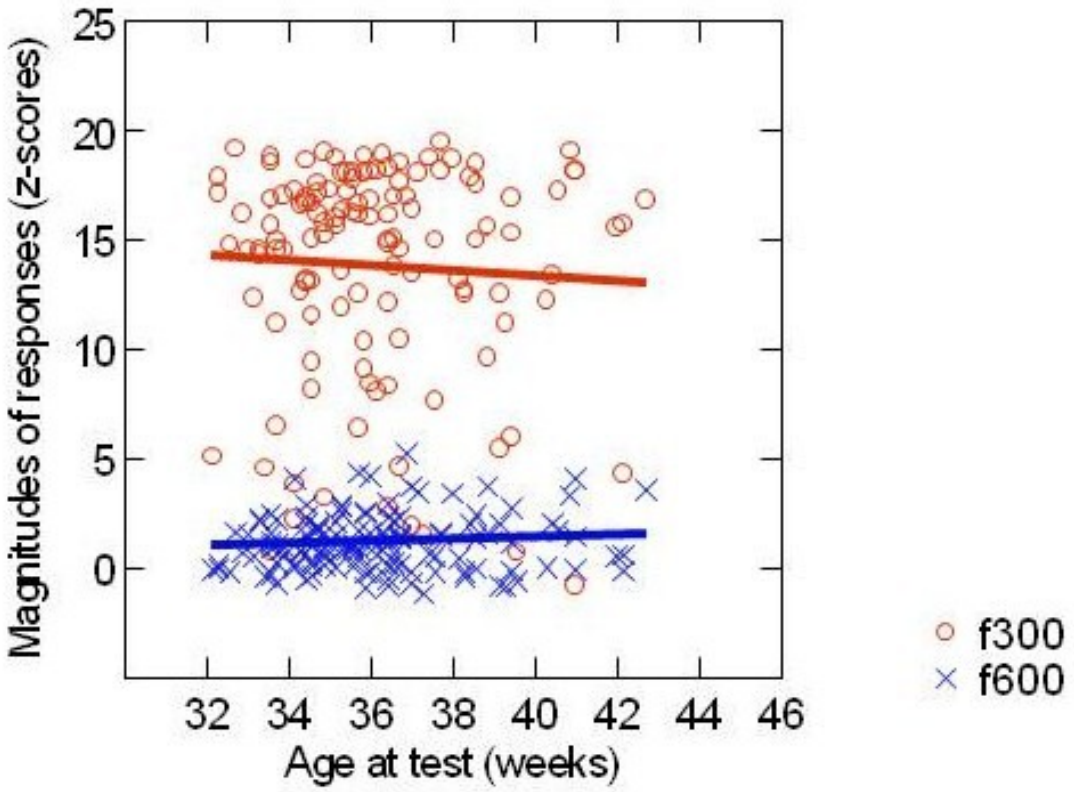

Figure 22. No significant difference across ages when examine the responses at f300, f600 in the sum spectra (1 outlier with age at test >45 weeks was removed). The best fitting linear functions for F300 and f600, provided for demonstration, were not significant across age.

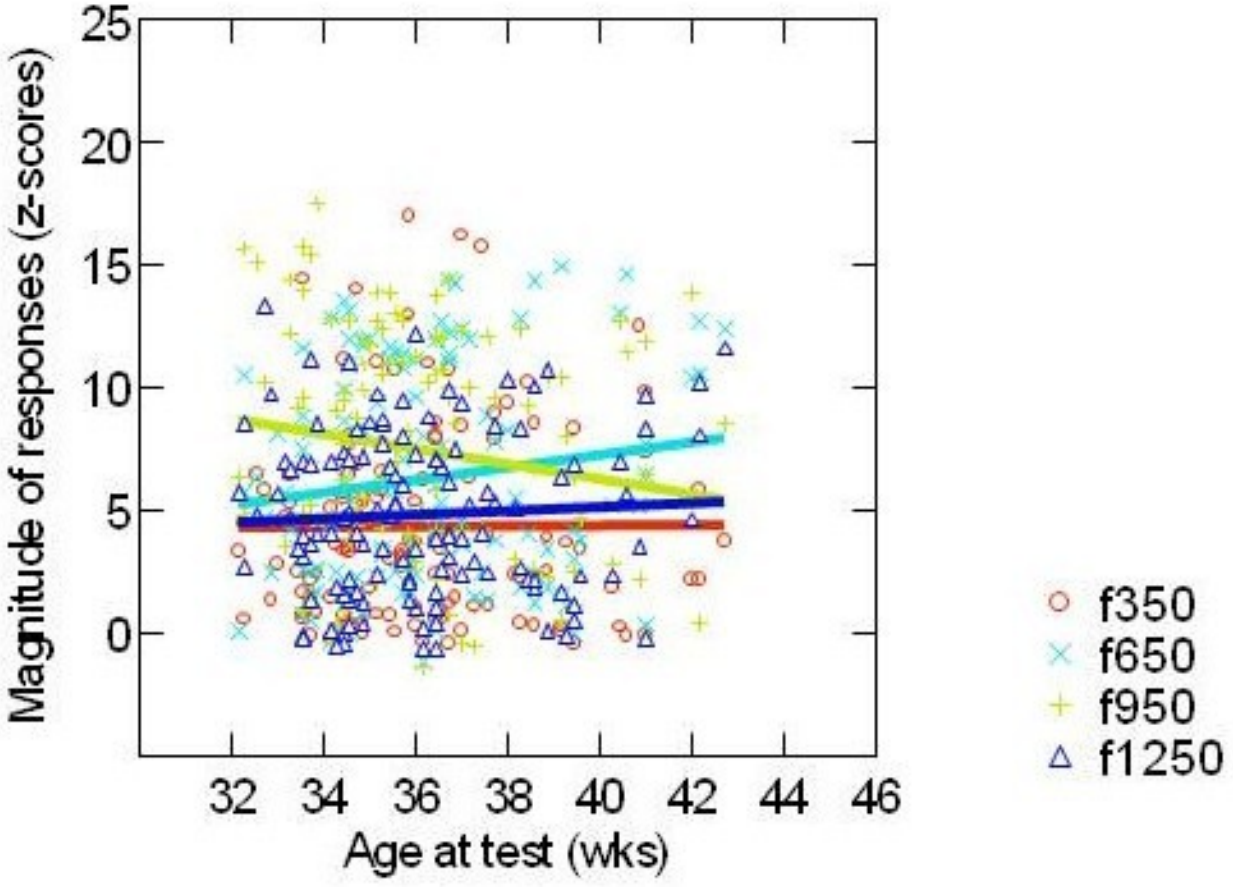

Figure 23. No significant difference across ages when examining the responses at f350, f650, f1250 in the difference spectra (1 outlier with age at test >45 weeks was removed). Linear fitted trend of the data is used.

Table 6. Responses at targeted frequencies across ages. No significant differences of the targeted frequencies in sum and difference spectra were found across ages.

Targeted frequencies	$F_{(1,126)}$	P value	r	r^2	Power	N (α =.05; power=.80)
f300 (in the sum spectra)	1.27	0.26	0.1	0.01	0.20	1024
f600 (in the sum spectra)	0.67	0.41	0.073	0.005	0.12	1470
f350 (in the difference spectra)	0.01	0.94	0.007	0.0001	0.04	131072
f650 (in the difference spectra)	2.06	0.15	0.127	0.016	0.30	484
f950 (in the difference spectra)	4.31	0.04 *	0.182	0.033	0.56	234
f1250 (in the difference spectra)	0.21	0.65	0.04	0.002	0.07	1646

(*) Bonferroni corrected level of significance: α/n=0.05/4=0.01

C. Power analysis

For analyses in which the difference in magnitudes of responses was regressed upon age, the sample size of 128 subjects afforded 81% power to detect an effect with an R^2 of 0.06; that is, an effect explaining as little as 6% of the dependent variable's variance could be detected 80% of the time, using a two-tailed test with a significance level α of .05.

Using the calculated effect R^2 for responses at each targeted frequencies regressed upon age, we could determine the power of the analyses. Sample size (per cell) was also estimated for these analyses to reach a power of .80 with a significant level α of .05(see table 6).

III. Effect of brain insult on FFR

When we examined only infants with definite structural evidence of BI (n=10) compared to normal (no structural or functional evidence of BI) (n=58), we found that there were significantly lower responses from the BI group at f300 $F_{(1,66)}$=5.088 (P<0.03) and its harmonics in the sum spectra $F_{(1,66)}$=5.686 (P<0.02). Figure 24 displays the group difference in the means of responses at f300. Similarly, differences between the 2 groups in the mean responses to f600 are shown in Figure 25a. We noticed that the responses to f600 are low (z-scores of 1.341±1.36 versus 0.267±1.001 in the normal and structural BI, respectively. Also see table 3 and Figure 8 for the distribution of f600 in the total sample). A box and whisker graph in Figure 25b further illustrates the difference between the two groups. In the difference spectra, responses to f350 were lower in the BI group compared to normal ($F_{(1,66)}$=5.002 (P<0.03)) (see Figure 26).

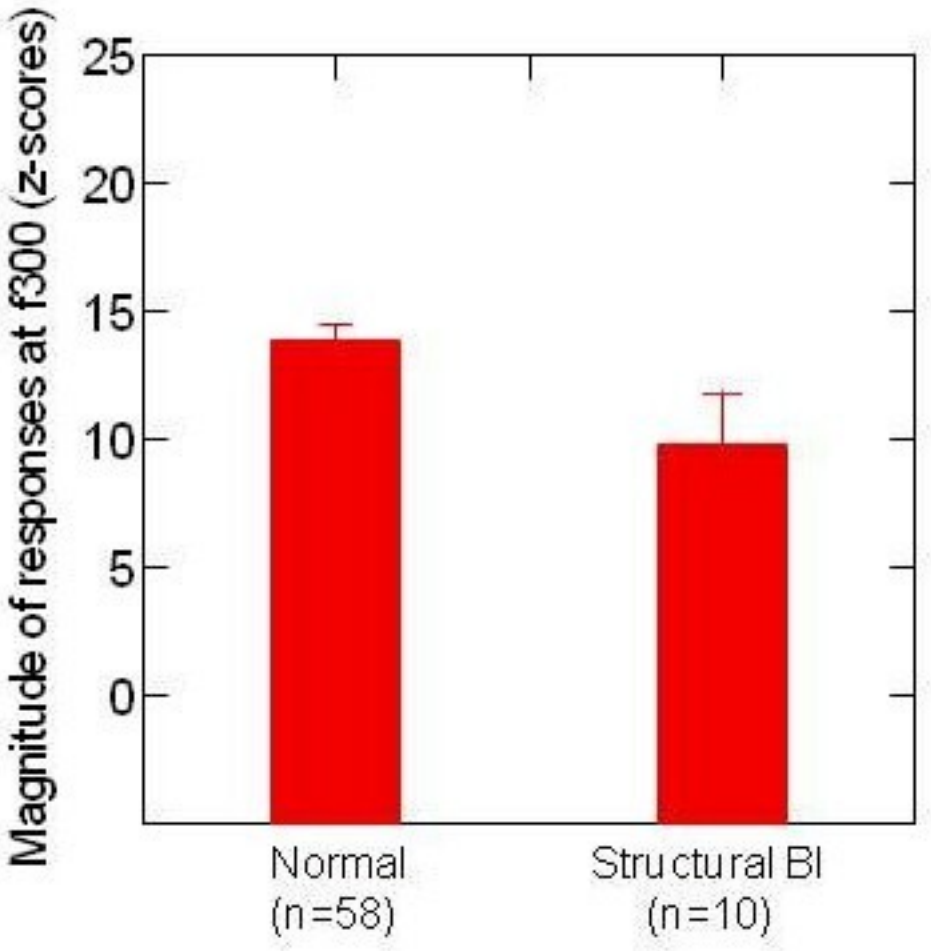

Figure 24. Structural BI infants have significantly lower responses at f300 compared to normal infants in the sum spectra $F_{(1,66)}$=5.088 (P<0.03). Error bars represent standard errors of the mean.

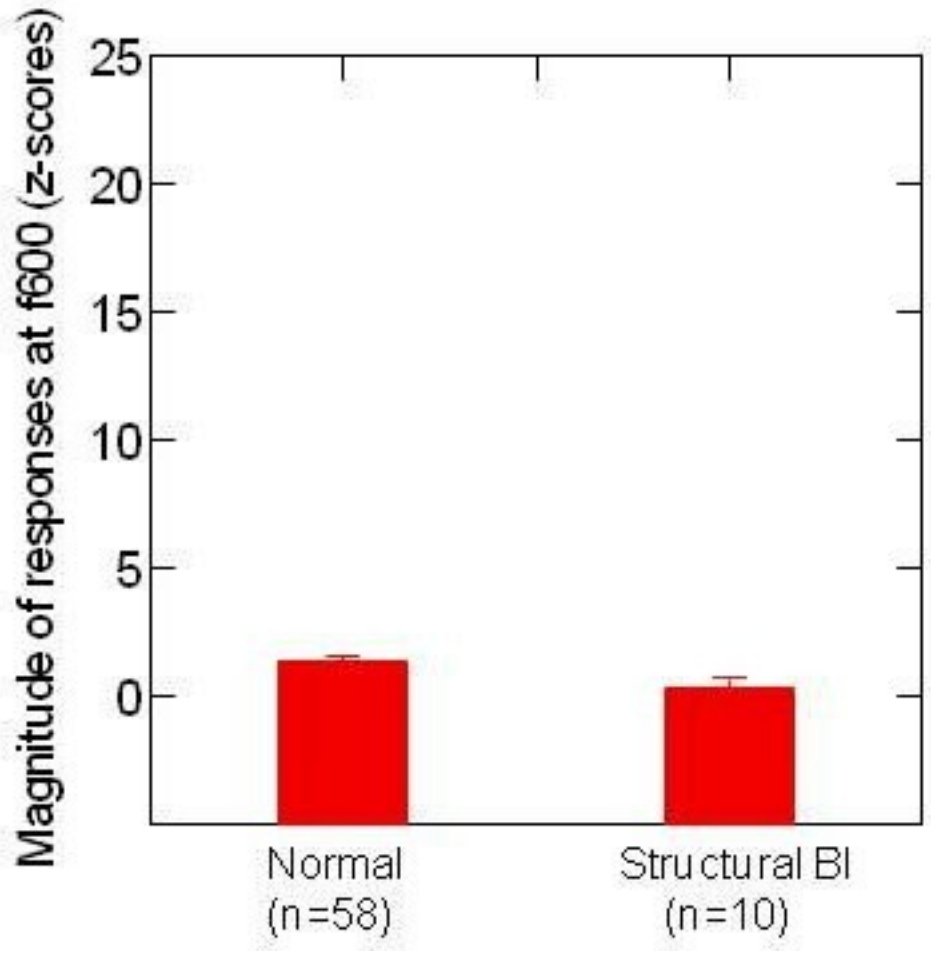

Figure 25a. Structural BI infants have significantly lower responses at f600 compared to normal infants in the sum spectra $F_{(1,66)}=5.69$ ($P<0.02$). Error bars represent standard errors of the mean.

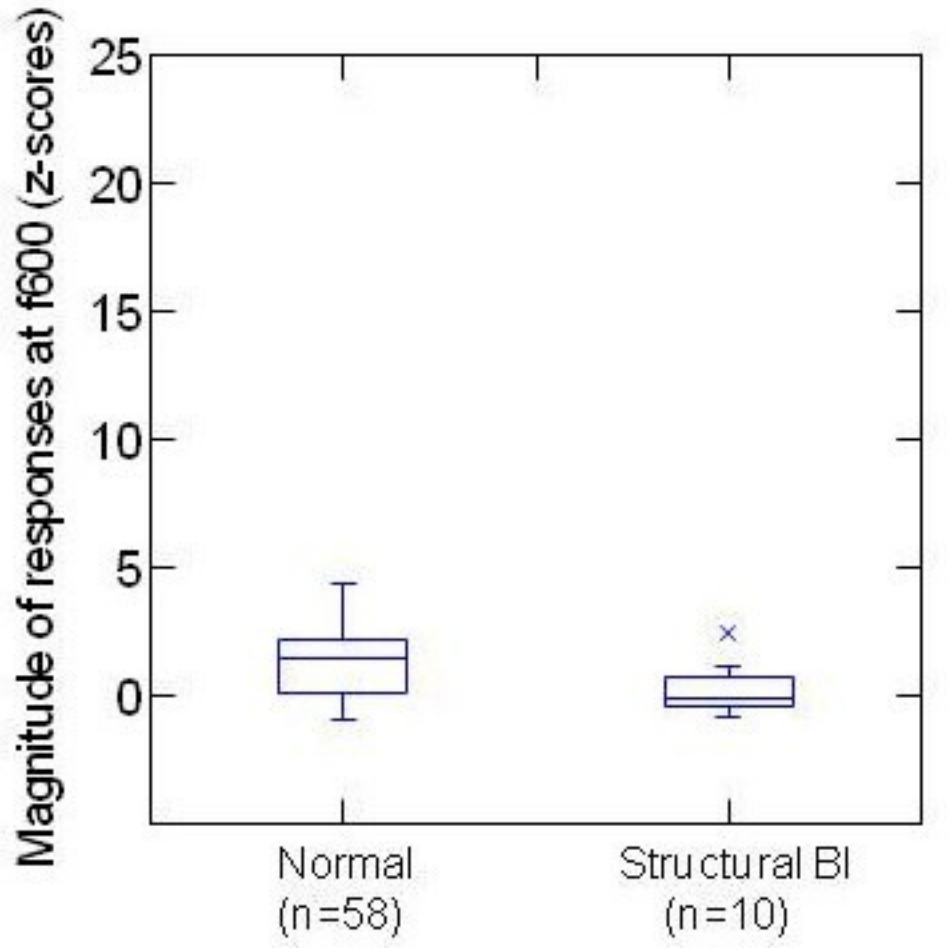

Figure 25b. Density display of responses at f600 in normal versus structural BI groups in the sum spectra. Line in the box represents the median. The "whisker" part of the graph shows the quartile range.

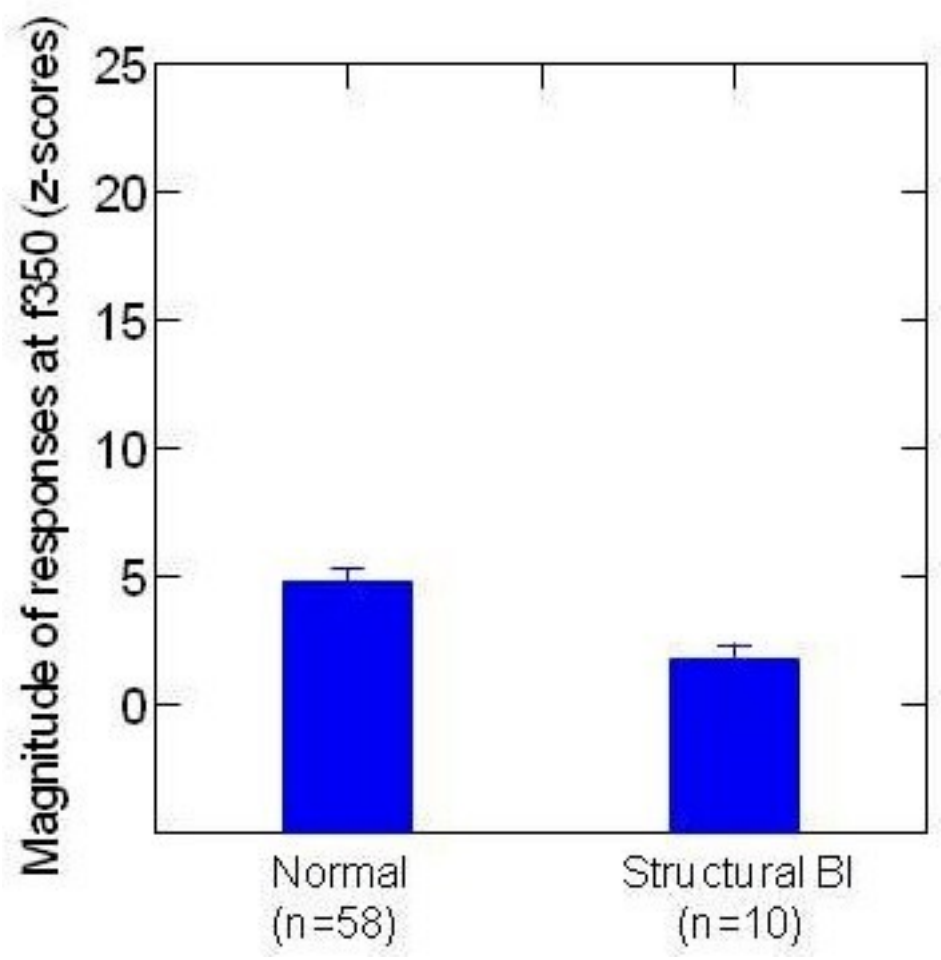

Figure 26. Significant lower responses at f350 in the structural BI group compared to the normal group in the difference spectra ($F_{(1,66)}$=5.002 (P<0.03). Error bars represent standard errors of the mean.

IV. No effect of abnormal-ABR-only on the responses to targeted frequencies

When we compared abnormal-ABR-only (n=60) versus normal (n=58) groups we did not find any significant differences in the responses to ER-related (f300) ($F_{(1,116)}$=0.295 (p<0.59)) and its harmonic (f600) ($F_{(1,116)}$=0.486 (p<0.49)) in the sum spectra. Histogram of responses to f300 and f600 in these 2 groups are displayed in Figure 27. Similarly, in the different spectra, abnormal-ABR-only and normal groups were not different in responses to DP-related (f350)

($F_{(1,116)}$=0.386 (p<0.54)) as well as to stimulus components at f650 ($F_{(1,116)}$=0.003 (p<0.96)); at f950 ($F_{(1,116)}$=0.016 (p<0.9)) and at f1250 ($F_{(1,116)}$=0.02 (p<0.89)) (see histogram in Figure 28)

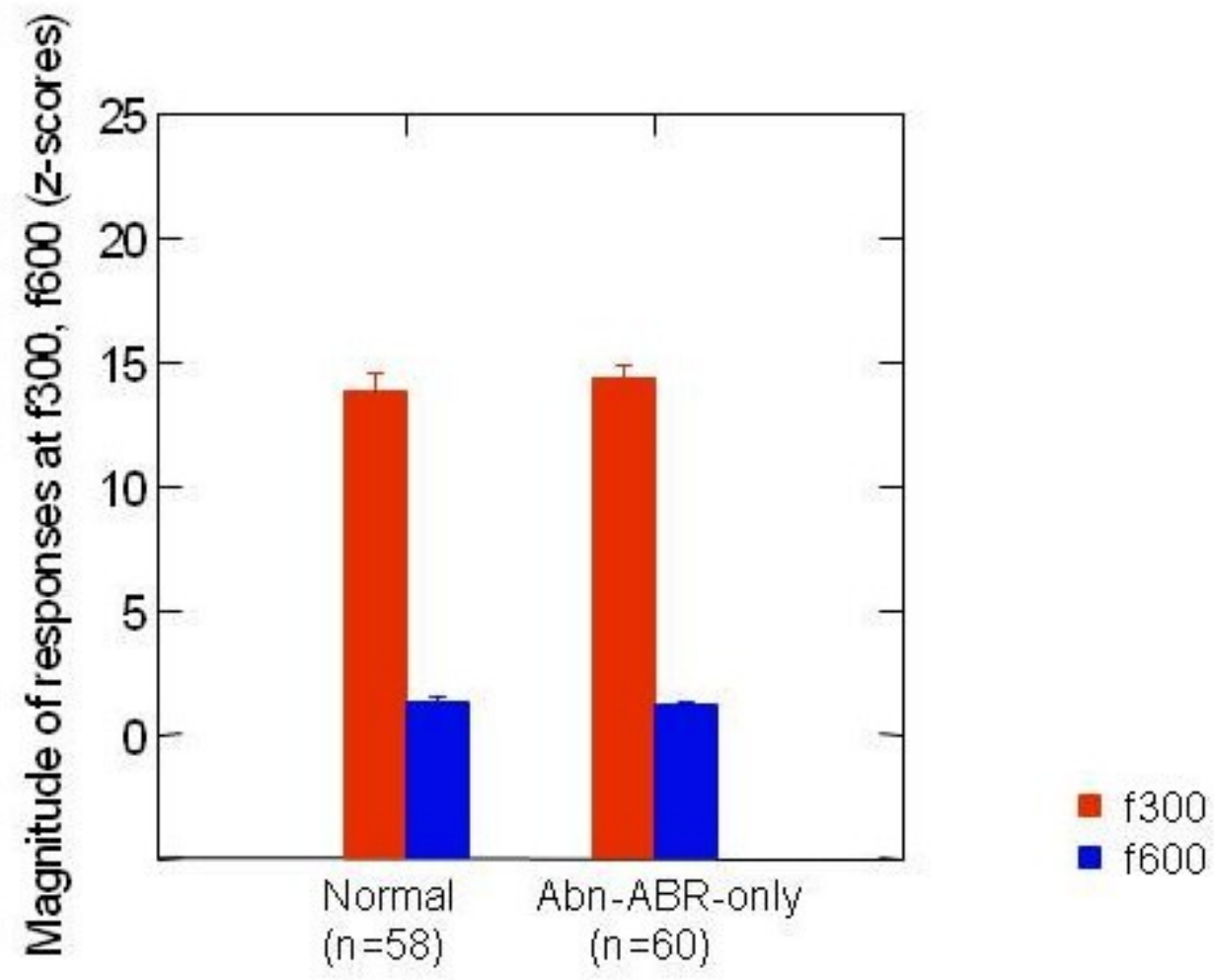

Figure 27. No significant differences in the responses between normal and abnormal-ABR-only groups in the sum spectra at f300($F_{(1,116)}$=0.295 (p<0.59)) and at f600 ($F_{(1,116)}$=0.486 (p<0.49)). Error bars represent standard errors of the means.

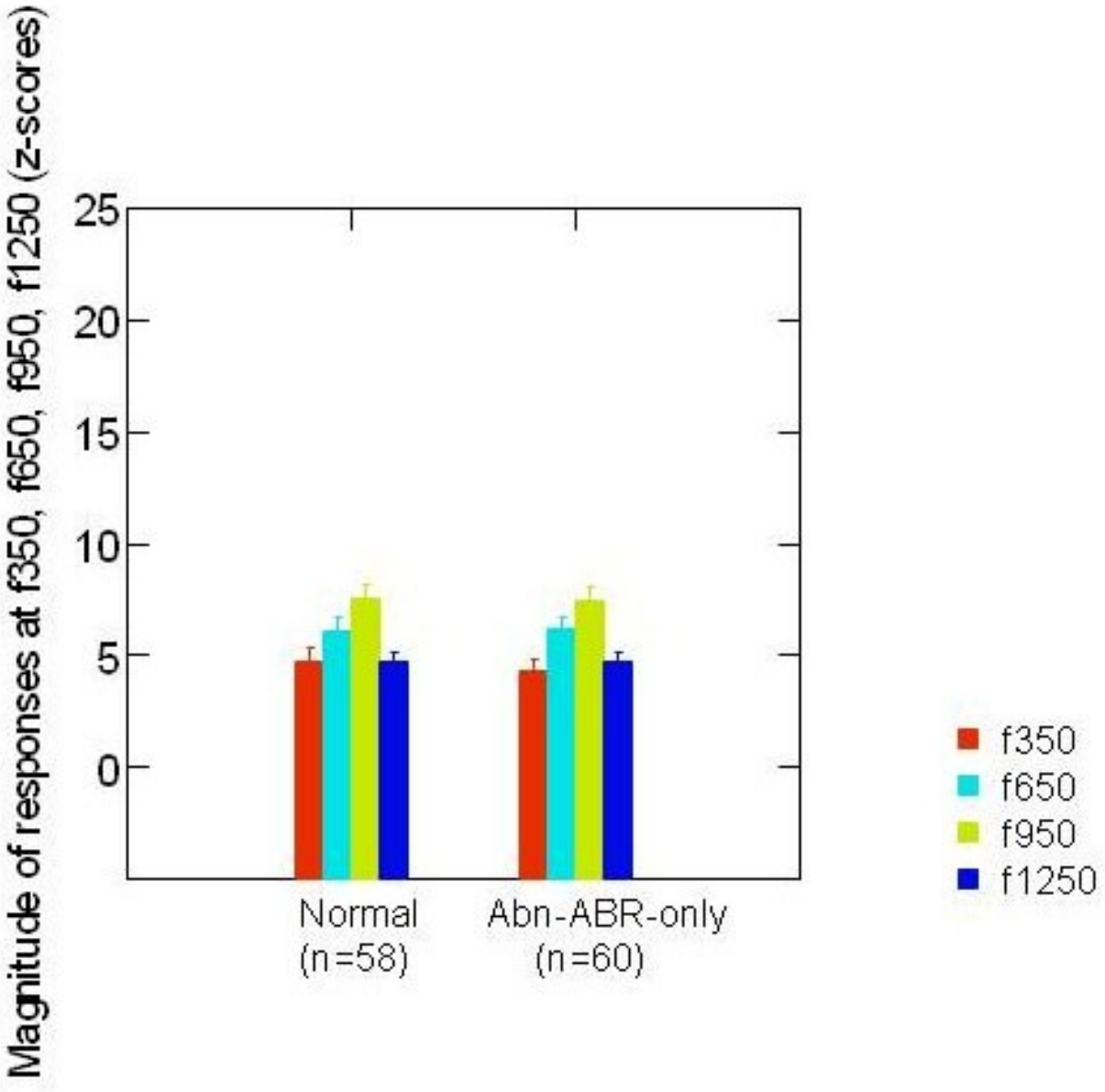

Figure 28. No significant differences in the responses between normal and abnormal ABR only groups in the difference spectra at f350($F_{(1,116)}$=0.386 ($p<0.54$)); at f650 ($F_{(1,116)}$=0.003 ($p<0.96$)); at f950 ($F_{(1,116)}$=0.016 ($p<0.9$)); at f1250 ($F_{(1,116)}$=0.02 ($p<0.89$)). Error bars represent standard errors of the means.

V. No effect of gender on the responses to targeted frequencies

When gender was included as a covariate in all analyses we did not find any significant effect as well as interaction with other main effect on responses to the targeted frequencies.

In summary when age and CNS injury effects were examined we found that age was an unlikely differentiated contributor to our findings. Nor were any significant gender effect found. CNS insults, on the other hand, appeared to produce significant adverse.

CHAPTER 4 - DISCUSSION AND CONCLUSIONS

I. Development of the auditory processing of a MF complex tone

This thesis characterizes responses to a complex tone with MF in newborn infants. It appears that the responses to the envelope waveforms as well as to difference tones and the tonal complexes are present as early as the time we tested (32 weeks of gestation). Early maturation of the human auditory system has been well reported in numerous studies. Anatomically, myelination, as evidence of neuronal functional maturity, has been observed in various subcortical structures, e.g. cochlear nucleus, superior olive, lateral lemniscus, inferior colliculus in histological studies (Moore et al, 1995)and medial geniculate body in MRI studies (Counsell, 2002) by the 28-29th week of gestation. Other measures, such as behavioral, physiological, psychophysical experiments have shown early auditory functions in human fetuses. External sounds can produce change in heart rate and fetal movement from the 28th week of gestation (Lecanuet et al., 1995). No detectable difference across age was found in cochlear maturation measured by transient evoked otoacoustic emissions (Gkoritsa et al., 2007). Moreover, studies in fetal hearing has shown that by 33 weeks of gestation, responses to low frequency sounds (up to 1000Hz) are present (Hepper and Shahidullah, 1994). Human fetuses, when tested at 35 weeks old, are able to discriminate pure tones with different low-frequencies (i.e, 250 vs 500 Hz) and speech syllables (Shahidullah and Hepper, 1994; Lecanuet et al., 1995) as well as complex sounds in musical notes (Kisilevsky, 2004). These functions are thought to be mediated at the sub-cortical (Joseph, 2000), or higher level (Morokuma et al, 2004; Jardri et al, 2008). Thus, the observation in this study has confirmed the availability of necessary information for infants' processing of complex sounds in lower frequency range. This takes place at around 32 weeks gestational age, and remains stable across ages during the first months of life.

In contrast, functional maturation might be expected since orderly differences across age have been found in the absence of any CNS pathology in OAE measures of cochlear maturation (Jedrzejczak et al, 2007), ABR component latency and interpeak interval differences (Hecox et al., 1981; Karmel et al., 1988), and in fetal ABRs using magnetoencephalographic study (Holst et al., 2005).

One of the possible explanations for this discrepancy could be due to selected methodology and data analyses. With the sample size of this study and group data analysis, we were unable to achieve enough power to detect even small effects associated with gestational age. However, increasing the sample size is unrealistic. Longitudinal study and individual data analysis may offer a better study design for future research. For instance, in a study examining the development of pitch change detection using mismatch negativity, an electrophysiological technique, Kushnerenko et al. (2001) showed no differences across ages when examining group data. However a developmental trend was found when studying individual data longitudinally.

Pitch-related information encoded in FFR responses has been reported recently to be language-experience dependent in adults. Tonal language speakers had showed enhanced FFR responses to language relevant pitch-contours when compared to non-native speakers (Krishnan et al., 2005; 2009). Cross-sectional research of FFR in infants, as in our study, would make it difficult to detect experiential effects. The role of experience in infant studies is evident only thru intrauterine experience where mother's voice is presumed experienced resulting in a preference for "mothereses", where there's a distinct pitch changes. Longitudinal research and within subject data analyses in future studies would further address these developmental issues.

Relating to pitch perception, one purpose of this study was to examine the pitch extraction process. However with the current methodology, we were unable to answer this question directly. Although Greenberg et al. (1987) reported responses in the FFR difference spectra corresponding to psychophysical MF pitch percept in adult subjects, Wile and Balaban (2007) failed to duplicate this finding in a well-controlled study using a large sample.. Unlike their studies, our research lacks psychophysiological data to confirm the behavioral pitch percept. Moreover with no masking of the low frequency components, the peaks at around MF, if detected, may be due to difference tone interaction in the cochlea (Plack & Oxenham, 2005). Yet it was suggested that information from the envelope and component related frequencies were weighted to derive pitch information (Wile & Balaban, 2007). On the other hand, if the same pitch extraction mechanism is utilized in infants then the results in this study suggest the capability to synthesize pitch in newborns. Future studies incorporating behavioral observations and including masking of combination tones in the MF range might allow us to address whether newborn infants are capable of hearing out the pitch of complex tones with MF the same way as adults do.

II. Effect of brain insult on auditory processing of complex sound

The second question of interest in this study is the neural mechanism underlying this processing of complex sound. Infants with definite structural evidence of BI had significantly lower responses to the envelope-related and the distortion product-related frequencies when compared to normal infants (no structural or functional evidence of BI). All of the infants in our study had passed the hearing screening using OAE. To our knowledge, this is the first evidence

of atypical auditory processing of complex sounds in infants with structural evidence of BI during the newborn period. Atypical ERP auditory processing of speech sounds and tones has been reported in premature infants at term age (Kurtzberg et al., 1984; Fellman et al., 2004), although evidence of BI was not documented.

In both preterm and term infants, hypoxia/ischemia (HI), a reduction in blood oxygenation and blood flow, is a common cause of insults to the perinatal brain. CNS insults caused by HI (e.g., hemorrhage, infarct, encephalopathy) often affect subcortical structures (Fawer et al., 1983; Volpe, 2001). The auditory structures and pathways, in adjacent to these areas, could be affected (Majnemer, Rosenblatt & Riley, 1990) and is reflected in ABR recordings (e.g, Karmel et al., 1988; Edwards et al., 1985; Hecox et al, 1981; Henderson-Smart et al., 1983; Ito, 1984; Stockard et al., 1983). FFR recorded in this study was thought to include contributions from hair cell dynamics, cochlear mechanics, and phase-locked coding of neural activity to low frequency signals (below about 2 kHz) in the auditory system (Galambos, Makeig & Talmachooff, 1981; Patel & Balaban, 2000; John & Picton, 2000). If normal cochlear function is assessed sufficiently using OAE, the lower FFR responses in BI compared to normal infants in our study could be due to the disruption of phase-locking capability of the auditory neurons. Certain classes of these neurons must be selectively affected in perinatal BI because only FFR responses to the envelope-related and distortion product-related are impaired. Neurophysiological studies suggested that two classes of ventral cochlear nucleus (VCN) neurons, namely primary-like and sustained chopper units, preserve the temporal input from the auditory nerve, as well as connect to the inferior colliculus, thus have the capability of encoding pitch-related information(e.g., Shofner, 1991,1999, 2008; Wiegrebe & Meddis, 2004). Neural cells of VCN are especially susceptible to anoxia (Dublin, 1982). Interestingly, infants with

abnormal ABR only (without structural evidence of BI) are not significantly different in their FFR response when contrasted to the normal group. This observation suggests several possibilities: 1) there exist different underlying mechanisms for ABR and FFR thus they provide different information about auditory function integrity (e.g., auditory neural transmission versus auditory neural phase-locking capability); 2) the relatively small sample size of the BI group could be a caveat for the insignificant differences in ABR.

III. Implication for development

Follow-up studies in high-risk infants have indicated a strong relation between CNS insults and developmental deficits in later years. The poor developmental outcomes in these BI infants not only involve gross and fine motor skills, but also cognitive, attention and language development (e.g., Fawer & Calame, 1991; Graziani et al, 1985; Hack et al, 1994; Jongmans et al, 1997; Prechtl et al, 1997; Sostek et al, 1987; Gardner & Karmel, 1983; Karmel et al., 1991; Wallace et al, 1995). Premature infants with periventricular BI at school ages showed auditory temporal processing deficits in judgment of tonal order, reading and spelling (Downie et al., 2002, 2005). Aberrant language processing in former BI premature infants has been reported in a MRI study (Patterson, 2002). Term infants suffered from HI/asphyxia at birth also show speech impairment (Largo et al., 1986), and deficit in language skills (Robertson and Finer, 1985). The underlying mechanism of the observed deficits could be due to the persisting disturbances of early BI to brain structures and functional neural connections development. Peterson and colleagues (2000) reported the association of perinatal IVH and small volume of cerebellum, and left caudate nucleus in school age children. Moreover, differential brain activation in auditory task has been observed in ex- preterms with corpus callosum abnormality compared to term and

preterm controls (Santhouse et al, 2002). Not only in premature, but also in HI term infants, severe basal ganglia and white matter regions were found to correlate with developmental scores at 9-14 months (Haataja et al, 2001).

Taken together, atypical auditory processing of complex sounds in infants with structural evidence of perinatal BI reported in this study could serve as an indicator for high-risk of developmental sequelae. These infants would be beneficial from a careful developmental follow-up and early intervention.

In conclusion, our study reported the presence of auditory processing of complex sound in newborn infants at the time of the test, as early as 32 weeks gestation. This processing remains stable across age during the first month of life. Moreover, infants with structural evidence of perinatal brain injury, but not those with abnormal ABR only, showed impairment in this type of auditory processing.

Appendix 1. Paired t-tests comparing f300 to each of its neighboring frequencies (f292 … f308)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	f300-f292	12.61	5.15	.45	11.71	13.51	27.71	127	.000
Pair 2	f300-f294	12.92	5.14	.45	12.02	13.82	28.45	127	.000
Pair 3	f300-f296	10.74	4.15	.37	10.01	11.47	29.27	127	.000
Pair 4	f300-f298	7.02	3.33	.29	6.43	7.60	23.81	127	.000
Pair 5	f300-f302	11.98	4.78	.42	11.15	12.82	28.33	127	.000
Pair 6	f300-f304	11.63	4.24	.37	10.89	12.37	31.00	127	.000
Pair 7	f300-f306	12.15	4.67	.41	11.33	12.96	29.40	127	.000
Pair 8	f300-f308	13.02	5.39	.48	12.07	13.96	27.34	127	.000

Appendix 2. Descriptive statistics of the differences in means of pairs comparing f300 to each of its neighboring frequencies (f292…f308)

	N	Minimum	Maximum	Mean	Std. Deviation
f300 f292	128	-2.43	19.00	12.61	5.15
f300 f294	128	-2.31	18.78	12.92	5.14
f300 f296	128	-.98	15.99	10.74	4.15
f300 f298	128	-2.59	11.85	7.02	3.33
f300 f302	128	-2.22	17.34	11.98	4.78
f300 f304	128	-2.36	16.76	11.63	4.24
f300 f306	128	-3.24	17.92	12.15	4.67
f300 f308	128	-4.25	19.32	13.02	5.39

Appendix 3. Paired t-tests comparing f600 and neighboring frequencies (f592…f608)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	f600-f592	1.03	1.31	.11	.80	1.26	8.91	127	.000
Pair 2	f600-f594	.92	1.45	.13	.67	1.18	7.21	127	.000
Pair 3	f600-f596	.97	1.27	.11	.75	1.19	8.62	127	.000
Pair 4	f600-f598	.08	.91	.08	-.08	.24	1.03	127	.303
Pair 5	f600-f602	1.15	1.34	.12	.92	1.39	9.73	127	.000
Pair 6	f600-f604	1.25	1.32	.12	1.02	1.48	10.70	127	.000
Pair 7	f600-f606	1.25	1.34	.12	1.016	1.48	10.54	127	.000
Pair 8	f600-f608	1.23	1.38	.12	.99	1.47	10.11	127	.000

Appendix 4. Descriptive statistics of the differences in means of pairs comparing f600 and neighboring frequencies (f592…f608)

	N	Minimum	Maximum	Mean	Std. Deviation
f600 f592	128	-1.71	4.48	1.03	1.31
f600 f594	128	-4.28	5.03	.92	1.45
f600 f596	128	-2.39	4.29	.97	1.27
f600 f598	128	-2.71	2.34	.08	.91
f600 f602	128	-1.81	5.13	1.16	1.34
f600 f604	128	-1.82	4.98	1.25	1.32
f600 f606	128	-1.77	4.63	1.25	1.34
f600 f608	128	-2.34	5.48	1.23	1.38

Appendix 5. Paired t-tests comparing f350 and neighboring frequencies (f342 … f358).

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	f350-f342	4.07	3.97	.35	3.37	4.76	11.59	127	.000
Pair 2	f350-f344	3.73	3.63	.32	3.09	4.36	11.61	127	.000
Pair 3	f350-f346	3.71	3.49	.31	3.10	4.32	12.01	127	.000
Pair 4	f350-f348	4.04	3.95	.35	3.35	4.73	11.57	127	.000
Pair 5	f350-f352	1.64	1.76	.15	1.33	1.94	10.51	127	.000
Pair 6	f350-f354	3.60	3.52	.31	2.98	4.21	11.56	127	.000
Pair 7	f350-f356	4.07	3.99	.35	3.37	4.77	11.52	127	.000
Pair 8	f350-f358	3.48	4.02	.35	2.78	4.19	9.79	127	.000

Appendix 6. Descriptive statistics of the differences in means of pairs comparing f350 and neighboring frequencies (f342 … f358)

	N	Minimum	Maximum	Mean	Std. Deviation
f350 f342	128	-1.35	16.36	4.06	3.97
f350 f344	128	-1.45	14.34	3.73	3.63
f350 f346	128	-2.92	14.95	3.71	3.49
f350 f348	128	-2.76	16.68	4.04	3.95
f350 f352	128	-2.73	7.12	1.64	1.76
f350 f354	128	-1.67	14.76	3.60	3.52
f350 f356	128	-1.66	16.90	4.07	3.99
f350 f358	128	-2.63	15.46	3.48	4.02

Appendix 7. Paired t-tests comparing f650 and neighboring frequencies (f642…f658)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	f650-f642	6.15	4.29	.38	5.41	6.91	16.24	127	.000
Pair 2	f650-f644	5.79	3.87	.34	5.12	6.47	16.95	127	.000
Pair 3	f650-f646	5.50	3.73	.33	4.85	6.16	16.69	127	.000
Pair 4	f650-f648	5.99	4.19	.37	5.27	6.73	16.21	127	.000
Pair 5	f650-f652	2.92	1.95	.17	2.58	3.26	16.98	127	.000
Pair 6	f650-f654	5.26	3.50	.31	4.65	5.87	17.01	127	.000
Pair 7	f650-f656	6.25	4.36	.38	5.49	7.01	16.22	127	.000
Pair 8	f650-f658	4.93	5.11	.45	4.04	5.83	10.93	127	.000

Appendix 8. Descriptive statistics of the differences in means of pairs comparing f650 and neighboring frequencies (f642…f658)

	N	Minimum	Maximum	Mean	Std. Deviation
f650 f642	128	-2.54	14.60	6.16	4.29
f650 f644	128	-.22	13.20	5.79	3.87
f650 f646	128	-1.17	12.91	5.50	3.73
f650 f648	128	-.18	13.86	5.99	4.17
f650 f652	128	-1.00	7.61	2.92	1.95
f650 f654	128	-.57	12.23	5.26	3.49
f650 f656	128	-1.02	14.81	6.25	4.36
f650 f658	128	-12.37	14.35	4.93	5.11

Appendix 9. Paired t-tests comparing f950 and neighboring frequencies (f942 … f958)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	F950-f942	7.59	4.58	.40	6.78	8.39	18.72	127	.000
Pair 2	f950-f944	6.96	4.23	.37	6.22	7.70	18.59	127	.000
Pair 3	f950-f946	6.38	3.91	.35	5.70	7.07	18.45	127	.000
Pair 4	f950-f948	6.58	3.81	.34	5.91	7.25	19.52	127	.000
Pair 5	f950-f952	4.61	2.74	.24	4.13	5.09	19.06	127	.000
Pair 6	f950-f954	6.32	3.62	.32	5.68	6.95	19.72	127	.000
Pair 7	f950-f956	7.41	4.43	.39	6.64	8.18	18.94	127	.000
Pair 8	f950-f958	7.49	4.63	.41	6.69	8.31	18.30	127	.000

Appendix 10. Descriptive statistics of the differences in means of pairs comparing f950 and neighboring frequencies (f942 … f958)

	N	Minimum	Maximum	Mean	Std. Deviation
f950 f942	128	-1.02	17.50	7.59	4.58
f950 f944	128	-1.17	15.79	6.96	4.23
f950 f946	128	-2.04	14.83	6.38	3.91
f950 f948	128	-.85	15.22	6.58	3.81
f950 f952	128	-.52	10.62	4.61	2.74
f950 f954	128	-1.27	14.37	6.32	3.62
f950 f956	128	-.29	17.02	7.41	4.43
f950 f958	128	-2.42	16.93	7.49	4.63

Appendix 11. Paired t-tests comparing mean of responses at f1250 and neighboring frequencies (f1242 … f1258)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	f1250-f1242	5.05	3.38	.29	4.46	5.64	16.90	127	.000
Pair 2	f1250 - f1244	4.83	3.18	.28	4.28	5.39	17.21	127	.000
Pair 3	f1250 - f1246	4.35	2.76	.24	3.86	4.83	17.79	127	.000
Pair 4	f1250 - f1248	3.84	2.42	.21	3.42	4.27	17.96	127	.000
Pair 5	f1250 - f1252	3.85	2.45	.22	3.42	4.28	17.77	127	.000
Pair 6	f1250 - f1254	4.34	2.75	.24	3.86	4.82	17.84	127	.000
Pair 7	f1250 - f1256	4.85	3.08	.27	4.31	5.38	17.82	127	.000
Pair 8	f1250 - f1258	5.10	3.39	.30	4.51	5.69	17.00	127	.000

Appendix 12. Descriptive statistics of the differences in means of pairs comparing at f1250 and neighboring frequencies (f1242 … f1258)

	N	Minimum	Maximum	Mean	Std. Deviation
f1250 f1242	128	-1.08	13.27	5.05	3.38
f1250 f1244	128	-1.49	12.88	4.83	3.18
f1250 f1246	128	-.79	11.10	4.35	2.76
f1250 f1248	128	-.59	10.32	3.84	2.42
f1250 f1252	128	-.96	9.64	3.85	2.45
f1250 f1254	128	-1.45	10.62	4.34	2.75
f1250 f1256	128	-.44	12.30	4.85	3.08
f1250 f1258	128	-.66	13.70	5.10	3.39

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