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Maturation of Human Cochlear Mechanisms as Reflected in Distortion Product Emissions

by

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ABSTRACT

Development of the auditory system can be investigated by using the cochlear traveling wave delay. Auditory brainstem response (ABR) and otoacoustic emissions (OAE) have been used to estimate this delay in order to study the frequency dependent maturation of cochlear function in humans. Distortion Product Emissions (DPE) are a type of OAE. The DPE, unlike ABR, is a pre-neural measurement that does not include any synaptic component. Mean group delays can be estimated from the DPE phase-versus-frequency relationship (Kimberley et al., 1993). The present investigation used DPEs to estimate the round-trip travel time from 1.7 to 10 kHz from 3 groups of neonates: 30-33, 34-37, and 38-42 wks. conceptional age (CA); and an adult group. The results were consistent with the results from Kimberley et al. (1993) who found that as frequency increased round-trip travel time decreased. However, travel times in the youngest age group (30-33 wks. CA) were longer than for the older two infant groups (34-37 & 38-42 wks. CA). This difference may be attributable to changes or development in the middle ear. No significant differences in travel times were found between the 34-37 week CA infants and those of 38-42 week CA suggesting that some maturation is occurring up until 34 weeks CA. In comparison with the adults, the travel times from the two older newborn groups were not significantly different for either the high (7 & 10 kHz) or low (1.7 & 2.4 kHz) f_2 frequencies, however in the mid-frequency range (3.5 & 5 kHz) the travel times were shorter in newborns. This difference in the mid-frequency range may be attributable to standing waves in the ear canal in the adults which could decrease the intensity of the primary tones used and therefore increase the latency of the travel time in that range (Dreisbach & Siegel, 1995). The similarities in the travel times at the high and low f_2 frequencies suggest that the cochlea is adult-like by 34 weeks CA. This differs from the results of previous ABR studies which found that adult values were not reached until 3-6 months of age.

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DEDICATION

To Dianne, Matthew and Melissa

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Chapter 1. INTRODUCTION

OVERVIEW

The purpose of this study was to conduct an investigation of the development of the cochlear mechanisms using Distortion Product Otoacoustic Emissions (DPE). The DPE is a non-invasive measure of cochlear function recorded in the ear canal. A DPE is the cubic distortion product ($2f_1$-f_2) generated by stimulating the cochlea with two tones at the frequencies f_1 and f_2 (f_2>f_1). The area of the basilar membrane (BM) corresponding to the overlap or interaction of the stimulus tones f_1 and f_2 generates the emission (Furst et al., 1988) but the dominant contribution originates from the f_2 place (Brown & Kemp, 1984; Fahey & Allen, 1986; Brown & Gaskill, 1990; Brown et al., 1992). To record the DPE a probe is placed in the ear canal. This probe consists of a microphone and two speakers through which two low level tones (f_1 and f_2) are played. The tones are acoustically mixed in the ear canal and travel through the middle ear to the cochlea. The DPE is generated in the cochlea and reverse transmitted through the middle ear and into the ear canal. In order to determine if the signal recorded in the ear canal is an emission and not background noise, samples of the background noise are taken above and below the emission frequency. An emission is deemed to be present if the emission amplitude is higher than the level of the background noise.

This DPE measurement can be used to determine the mean group delay or traveling wave delay. These delays are estimates of the time taken for a signal generated in the ear canal to travel to the cochlea, specifically the place on the BM corresponding to the frequency of the stimulus tones, generate an emission and travel back to the ear canal (Kimberley et al., 1993; Brown et al., 1995). This estimate, often referred to as a round-trip travel time, is based on the change in phase of the DPE with the change in DPE

frequency. The DPE phase-versus-frequency relationship is dependent on the $2f_1$-f_2 generation site which is assumed to be the f_2 place.

It has been shown that DPEs can be recorded from infants, both term and preterm (Lafreniere et al., 1991; Lasky et al., 1992; Smurzynski, 1994; Brown et al., 1994) as well as adults (Gaskill & Brown, 1990). Therefore, travel times can be estimated from both preterm, term and adult subjects using DPE measurements. It is then possible to investigate mechanisms for the developmental changes in cochlear mechanics as suggested by some researchers (Rubel, 1978; Romand, 1987) and seen in derived band Auditory Brainstem Response measures (Eggermont et al., 1991).

The introduction will consist of seven sections. The first section will review the anatomy of the auditory system from external to inner ear with an emphasis on the structures of the inner ear. Physiology of the auditory system is reviewed in the second section. A sound traveling from the external to inner ear results in the development of a traveling wave. The discussion focuses on the traveling wave and the effects of both the passive and the active mechanisms of the inner ear. The third section will survey the different estimates of traveling wave delay. Different methods have been devised to measure travel times in the cochlea. These different methods of estimation will be reviewed, particularly emphasizing mean group delay from DPE measurements. An overview of the development of the peripheral auditory system from both an embryological and a developmental perspective makes up the fourth section. The embryology of the ear is followed from conception to term birth. The development of the auditory system as studied by four different types of measures: spontaneous otoacoustic emission, evoked otoacoustic emission, reflectance and the auditory brainstem response will be examined. The last two sections include a rationale and an outline for the present study which will investigate the maturation of human cochlear mechanisms as reflected in Distortion Product Emissions.

ANATOMY

The peripheral auditory system consists of three sections: the external ear; the middle ear, and the inner ear. These sections, illustrated in Figure 1.1, work together to allow us to localize and perceive sound. This in turn provides the ability to gather information and knowledge about our environment and the world around us.

The External Ear

The external ear consists of the pinna and the external auditory meatus. The pinna or auricle is a thin plate of cartilage that is attached to each side of the head and is covered by skin. Although ears come in different shapes and sizes, the pinna is characterized by the helix and lobule, the most noticeable part of the ear. The ear has an uneven topography with numerous pits, groves and depressions. The largest depression is the bowl-shaped concha with leads down into the opening of the external auditory meatus or ear canal. There is a flap of skin called the tragus with which we can close off the ear canal. The ear canal is a 2.5 cm long (in the average adult) tube that opens on one end and terminates with the tympanic membrane on the other. The canal is lined with a continuous layer of skin which covers both cartilage and bone.

The Middle Ear

The tympanic membrane which terminates the ear canal is the beginning of the middle ear system. The middle ear is a six-sided space that consists of four walls, a floor and an epitympanic recess or attic. This space contains the ossicular chain, which comprises the three smallest bones (ossicles) in the human body. The ossicles, namely the malleus, incus and stapes connect the tympanic membrane to the cochlea. The eustachian tube is a passage way from the middle ear space out to the nasopharynx that allows air exchange to equalize air pressure on both sides of the tympanic membrane.

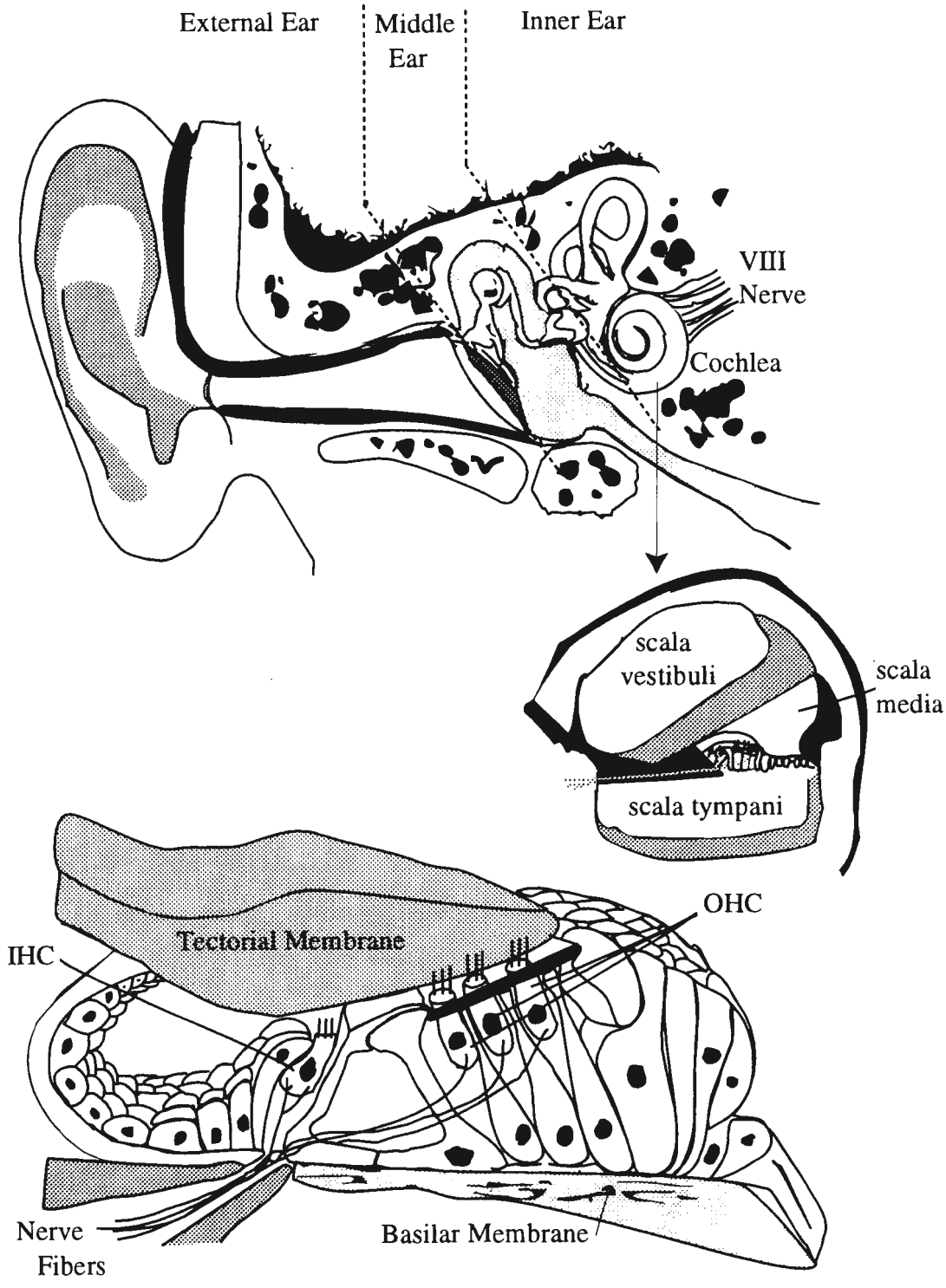


Figure 1.1 The Ear. (a) Schematic of the ear . (b) Cross-section of the cochlea. (c) Close up view of the organ of Corti.

The Inner Ear

The inner ear or cochlea is the sense organ for hearing. The human cochlea has a snail-like shape with two and a half turns around the center core or modiolus and if straightened out would be approximately 35 mm in length (Dallos, 1992). It is comprised of three ducts, scala vestibuli, scala tympani and scala media. The scala vestibuli and scala tympani join together via the helicotrema and are filled with perilymph fluid. The scala media is separated from the scala vestibuli by the vestibular (or Reissner's) membrane and from the scala tympani by the basilar membrane (BM). It too is a fluid filled duct but unlike the other two it is filled with endolymph. The cochlea is connected to the middle ear and communicates with it via two "openings" or "windows". The footplate of the stapes is connected to and takes up most of the oval window which opens into the scala vestibuli. The round window connects the scala tympani with the middle ear space and is a thin membrane that allows for compensation of the volume displacement produced when the stapes pushes in the oval window. Without this window, the movement by the stapes would be impossible because the fluid which fills the inner ear is incompressible.

Reissner's membrane's only function is to separate the endolymph from the perilymph. It is acoustically transparent and has no influence on the mechanical function of the cochlea. The basilar membrane is more important in that its mechanical properties control the passive linear components of the traveling wave. The basilar membrane as shown in Figure 1.2a is shaped like a wedge, with its narrowest part at the basal end and increasing in width towards the apex. With this increase in width, is a corresponding reduction in the stiffness of the basilar membrane.

Within the scala media and sitting on top of the BM is the organ of Corti, consisting of the tectorial membrane, inner and outer hair cells and numerous other supporting cells (see Figure 1.1). This scala is filled with endolymph, which is positively polarized and produced by the stria vascularis. The tectorial membrane is a gelatinous and fibrous flap

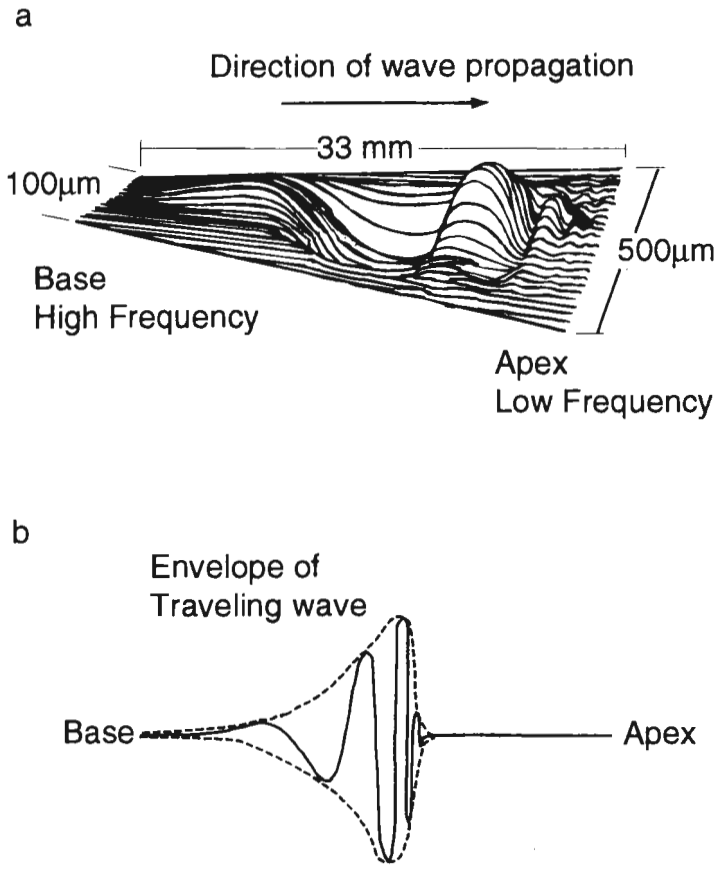


Figure 1.2 (a) A representation of a cochlear traveling wave from a three-dimensional model. (b) Diagram of the position of the BM at an instant in time during wave propagation (adapted from Harrison, 1988).

that is attached to the limbus by its inner edge. The space between the tectorial membrane and the reticular lamina, which sits below it, is filled with endolymph.

In the human cochlea there are approximately 12,000 outer hair cells (OHC) and 3500 inner hair cells (IHC) (Dallos, 1992). The IHCs are the sensory receptors for the auditory system and the OHCs are theorized to provide the motor force for the active process, which will be discussed later. These rows of hair cells run the length of the basilar membrane from base to apex allowing the cochlea to function as a mechanical frequency analyzer with the basal end being sensitive to the high frequencies and the apical end being sensitive to low frequency stimuli (Ryugo, 1992). Each OHC is surrounded longitudinally by a space which is filled with perilymph whereas the IHCs are surrounded by supporting cells (Dallos, 1992). Both IHCs and OHCs have a flat surface on top (cuticular plate) which contains a ciliary or sensory hair bundle. The tallest of the cilia from the OHC are embedded into the bottom surface of the tectorial membrane (Engström & Engström, 1978). At the base of each hair cell are synapses with the cochlear nerve fibers which consists of both afferent and efferent fibers. For the afferent neurons, 90-95% synapse only with IHC (the true sensory receptors) and the rest synapse with OHC (Dallos, 1992). Efferent fibers synapse mainly with the OHC but there are a substantial number of uncrossed afferents that synapse on the auditory fibers just below the IHCs.

Hair bundles are made up of rows of cilia linked together by filamentous linkages which sit on the apical end of the haircells (Hudspeth, 1989). The bundles have specific shapes, on the IHCs the cilia form a "U" shape whereas the OHCs may have a "W", "V" or "U" shape depending on their location along the basilar membrane. The tallest of the cilia from the OHCs are firmly attached to the underside of the tectorial membrane. The IHCs are not attached to the tectorial membrane. Movement of the cochlear fluid causes the basilar membrane to move up and down. This movement causes a shearing motion

between the tectorial membrane and the cilia on top of the haircells. Tip links connect the rows of cilia and cause this bundle of cilia to move together (Pickles, 1988).

During sound stimulation, the motion of the tectorial membrane and its direct connection with the OHCs alters the input to the IHCs by modifying the tectorial membrane-reticular lamina relationship (Zwislocki, 1990). The OHC connection to the tectorial membrane may cause a flow of endolymph around the cilia that are not attached to the membrane (Dallos, 1992). Deflection of the hair bundles opens and closes mechanically gated ion channels in the hair cells. These channels are located at or near the tips of the cilia and are controlled by "gating springs" (Hudspeth, 1989). The cells are directionally sensitive which means that excitation occurs when displacement of the hair bundle in the direction of the tallest cilia results in a stretching of the links. Inhibition occurs when the movement is in the opposite direction and the displacement is ineffective. This results in a change in the membrane potential which governs the release of a transmitter that depolarizes auditory nerve fibers and may produce action potentials.

PHYSIOLOGY

Sound Transmission through the External Ear

The peripheral auditory system consists of different sections, as shown in Figure 1.3, all of which play a part in the sense of hearing. The sensation of hearing may be evoked by a sound stimulus where sound pressure waves travel at the speed of sound (343 m/s) until they reach the external or outer ear. This section of the auditory system consists of the pinna, concha and external auditory meatus, and serves as protection for the tympanic membrane (Peck, 1994a) and to enhance the sound as it travels to the cochlea.

The human concha and ear canal increases the intensity of the sound over the frequency range 1.5 - 7.0 kilohertz (kHz) by way of a simple resonance (Wiener et al., 1966; Shaw, 1974). This increase has been shown to be as much as 10-20 decibels (dB)

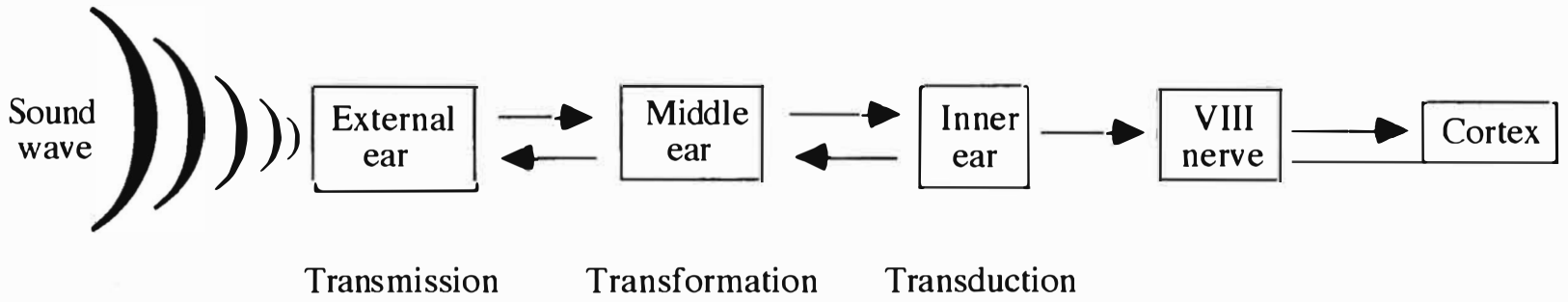


Figure 1.3 Block diagram of the sections of the ear.

sound pressure level (SPL) in the 2 to 5 kHz range (Shaw, 1974). This ear canal resonance is dependent on the size and shape of the ear canal. Adult ear canals are approximately 22-25 mm in length and have a diameter of 7.5 mm (Djupesland & Zwislocki, 1972, 1973; Zemplenyi et al., 1985). The length of the ear canal was measured from the umbo of the tympanic membrane to the entrance of the ear canal and does not include the concha. The resonant frequency of the ear canal is 2.6 - 2.7 kHz (Shaw, 1974; Kruger & Ruben, 1987) and is inversely related to its length. Using the assumption that the external ear is a simple one-quarter wave resonator, the "effective length" of an individual ear canal can be calculated using equation 1.0. Kruger (1987) calculated the effective length for the average adult (resonance = 2.7 kHz) to be 32 mm which is at least 25% longer than previously reported. This difference is likely due to additional "effective length" from the concha and pinna, which is calculated using:

$$f_0 = c/4L \qquad (1.0)$$

(where f_0 = resonant frequency; c = speed of sound; L = length of the canal).

There is only one reported study which evaluated the anatomical length of ear canals in term-born neonates, and they reported the length to be between 22 and 25 mm (McLellan & Webb, 1957). This measurement is from the pars tensa portion of the tympanic membrane to the outer surface of the tragus and thus includes the extra distance associated with the depth of the concha. Kruger and Ruben (1987) determined from the resonance frequency of 7.2 kHz that the "effective length" of an infant's (newborn to 37 months old) canal was 12 mm. This marked difference between measured length and calculated length may be due to the landmarks used in the measuring process. This difference in measuring technique might account for the lack of difference shown between neonates and adults.

Ear canal resonance has been shown to vary based on length and radius (Kates, 1988), canal geometry (Gilman & Dirks, 1986; Lawton & Stinson, 1986), "end effects" such as narrowing of the canal and ear drum incidence (Teranishi & Shaw, 1968) and

eardrum impedance (Zemplenyi et al., 1985). Infant's ear canals tend to be shorter and the tympanic membrane has a different incidence than in the adult, which would contribute to the increase in the resonant frequency. Kruger and colleagues (1987; Kruger & Ruben, 1987) found that the fundamental resonant frequency of the ear canal of newborns was 5.3 - 7.2 kHz or about 2 to 3 times higher than that of the average adult. This resonant frequency decreases markedly with age for the first two years of life at which time it reaches adult values. Bentler (1989) found that children between 3 and 13 years of age have resonant frequencies which are the same as those of adults. Dempster and Mackenzie (1990) contradicted this finding when they reported that the adult external auditory canal length was reached at age seven. Bentler (1991) has refuted their findings, saying that there were problems with the technique used in data collection, and in data analysis. However, both agreed that there was a wide range in the acoustical resonance of the external auditory canal in children and that ear canal resonance is age dependent.

Keefe et al. (1994) reported on diffuse-field to ear-canal sound pressure level transformation functions over frequency in infants from 1 to 24 months of age. They found that the resonant frequency decreased from 4.4 kHz at 1 month to 2.9 kHz at 24 months of age. Based on measurements of the diffuse-field transfer function and calculations based on their fit to a two-cylinder model, they estimated that a one month old would have an ear canal length of 14 mm and a concha length of 7 mm and that a 24 month old would have an ear canal length of 21 mm and a concha length of 9.8 mm. This would mean that based on Keefe et al.'s data, the "effective length" for a one month old would be 21 mm. This is significantly longer than Kruger and Ruben (1987) estimated but much closer to the anatomical measurements of 23.5 mm found by McLellan and Webb (1957). Keefe et al. (1994) stated that at 24 months the acoustic function of both the external and middle ears were not yet adult-like. Although there was only a small difference in resonant

frequency 2.9 kHz to 2.7 kHz ("effective length": 30.8 to 33 mm for the adult) there were larger differences in the diffuse-field absorption cross section.

The transfer function of the external ear will also differ if the sound source is placed in the ear canal. The use of an insert earphone blocks off the ear canal making the sound source closer to the tympanic membrane. This causes an upward shift in the frequency response of the average transformation of sound pressure level when compared to the transfer function from the ear canal entrance to the tympanic membrane. The shift in the peak response of the transfer function changed from 3.8 kHz to 7 kHz when using the insert ear phone (Shaw, 1974).

The use of insert earphones or a probe as the sound source will also be affected by standing waves in the ear canal. Standing waves result from sound which is not absorbed but reflected back from the eardrum. Theoretically, standing waves produce a spatially non-uniform pressure for frequencies above 2-3 kHz (Siegel, 1994). This means that the sound pressure at the eardrum would be underestimated near frequencies which correspond to the quarter-wave minima. Frequencies that correspond to the quarter wave phenomena will vary depending on the length of the tube. In the human ear, Siegel and colleague (1994; Siegel & Hirohata, 1994) pointed out that standing waves would cause up to a 20 dB underestimation of sound pressure at the eardrum in the 5-7 kHz region. Most of the standing wave problem below 10 kHz could be alleviated by placing the recording microphone close to the eardrum (5 mm).

Transformation by the Middle Ear

The sound has now traveled down the ear canal and impinges on the tympanic membrane causing it to vibrate. The vibrating of the tympanic membrane converts the sound into a mechanical vibration that is passed along to the ossicular chain and through the stapes to the inner ear. The middle ear system is a mechanical transformer used to help

compensate for the impedance mismatch between sound traveling through air and cochlear fluid. Approximately 28 dB (less for the low and high frequencies and more for the mid-frequencies) is lost when the middle ear is removed (Wever & Lawrence, 1950). The proportion of sound pressure that is transmitted through the middle ear can be calculated by the equation:

$$X = 4Z_bZ_a/(Z_b + Z_a)^2 \qquad (1.1)$$

where Z_a is the impedance of air and Z_b is the cochlear input impedance. The air to cochlea mismatch is caused by the much larger cochlear input impedance which allows about 3% of the signal amplitude (sound energy) to be transmitted into the cochlea and 97% is reflected (Durrant & Lovrinic, 1977).

The middle ear has three mechanisms which help correct this mismatch in impedance. The first is the effective area which is the difference between the area of the tympanic membrane and the oval window. The area ratio of the tympanic membrane (55.0 mm^2) is 17 times (55/3.3) greater than that of the stapes footplate (3.2 mm^2). The second is the leverage action of the ossicular chain which contributes a factor of 1.3/1 (Yost & Nielsen, 1985). These two methods increase the sound pressure by 22/1 or 22 times (17*1.3) which equates to approximately 27 dB. The third principle, a relatively small factor, is the conical shape of the tympanic membrane. The tympanic membrane moves in and out in relation to the sound and as it does it buckles causing the arm of the malleus to move less than the surface of the membrane (Khanna & Tonndorf, 1972; Pickles, 1988). However, only about 60-65% of this sound energy is transferred by the middle ear system. In addition, the middle ear is not equally efficient at all frequencies (Harrison, 1988). In man it is most efficient below 2.5 kHz where our hearing is most sensitive and decreases in the high frequencies.

However, these classic mechanisms have been shown to be inadequate to explain the loss of transmission due to the mismatch in impedance between air and cochlea. Killion

and Dallos (1979) used a model of the external and middle ear system where the oval window was considered to be the equivalent of a small piston mounted in an infinite baffle (the head) and found the mismatch to be frequency dependent. Using the equation:

$$Z_R \approx j\ (16\delta /3\pi a)f \qquad (1.2)$$

where Z_R is the acoustic radiation impedance, δ is the density of the air, a is the equivalent radius of the piston and f is the frequency of interest. The amount of pressure required to match the acoustic input impedance for the cochlea was calculated by determining the perfect impedance match from $P_c = P_d N/(2)^{1/2}$. They were able to show that more than 50 dB would be needed at 100 Hz to compensate for the mismatch and this is significantly greater than the 28 dB reported by Wever and Lawrence (1950). Killion and Dallos (1979) conclude that the combined action of the external and middle ears is necessary for a good impedance match with which to compensate for the loss of energy. In the human adult this would happen at approximately 2.7 kHz due to the resonance of the external ear.

The ossicular chain carries the vibratory pattern of the sound to the inner ear. The first bone is the malleus which attaches to the tympanic membrane. Rhode (1978) studied the frequency response of the ossicles in the squirrel monkey and found that the response of the malleus had the greatest variation in the low frequencies and least in the 2 to 5 kHz range. The phase and amplitude responses measured at the incus were relatively flat to 10 kHz but they were approximately 6 dB less than that of the malleus. The stapes movement has been observed in the 1930's and 40's by researchers such as von Békésy (from Zwislocki, 1984), and Stevens and Davis (1938). They observed the stapes rocking like a lever with the footplate acting as a fulcrum. However, more recent investigations by Guinan and Peake (1966) and Rhode (1978) disagreed with the rocking motion and believed that it was caused by the large intensities and displacements that were necessary for the researchers to be able to view the motion in cadavers. Additional information from Guinan and Peake (1966) indicated that in the cat there was support for the idea that the

stapes moves with a "piston-like" motion in and out of the cochlea. They found that the ossicular chain rotates as a single rigid body with an axis of rotation oriented in an anterior-posterior direction. The stapes displacement is basically linear for sound pressure levels below 130 dB for the frequency range up to 2.0 kHz and for even higher sound pressure level above 2.0 kHz. In other words, if the sound pressure is raised 10 dB then the stapes displacement changes in amplitude by 10 dB. Moller (1974) stated that if these conditions were valid in man then the middle ear is to be regarded as a linear system which does not produce any distortion components in ordinary sounds. The displacement above these limits is considered to be nonlinear.

Peake et al. (1992) indicated that the middle ear coupled sound from the ear canal to the cochlea. They described it using the following formula:

$$U_S = \frac{P_{IS} + P_{WD}}{Z_{SC}} \qquad (1.3)$$

The sound pressure in the external ear canal creates a volume velocity at the tympanic membrane, which moves through the ossicles and creates a volume velocity at the stapes (U_S). In turn, this velocity is related to the volume velocity of the round window through the cochlea. This difference between the stapes and round window is termed "acoustic coupling". The velocity of the stapes is determined by the sum of the pressures from the ossicular chain (P_{IS}) and the cochlear windows (P_{WD}) and the impedance of the cochlea (Z_{SC}). Therefore, the velocity of the stapes is dependent on a number of factors, including the sound pressure of the signal, the tympanic membrane velocity, the pressure exerted by the ossicular chain, the middle ear, the round window and the impedance of the cochlea. Because all these factors are frequency dependent the spectrum of the signal can change the velocity of the stapes according to its relationship to the above formula.

Cochlear Mechanics and the Inner Ear

Since Békésy's initial observations of the traveling wave, the BM movement has been monitored by methods which include the Mössbauer technique (Johnstone & Boyle, 1967; Sellick et al., 1982), the capacitive probe technique (Wilson & Johnstone, 1975), and laser interferometry (Khanna & Leonard, 1982). Results from these studies confirmed that the BM was mechanically tuned but also found it to be sharply tuned. It was discovered that if the cochlea was in good physiological condition then sharp tuning was present but if the cochlea was in poor condition the sharp tuning would disappear (Pickles, 1988).

The sound wave has traveled through the external and middle ears and is on its way to being perceived as sound. As it passes through the middle ear via the vibration of the ossicular chain, the motion of the stapes sets up a traveling wave in the fluid of the scala vestibuli at the frequency of the sound. The movement within the inner ear can be described by two components: passive and active cochlear mechanics.

Passive Linear Mechanics

Passive Linear Mechanics consists of the traveling wave and its interactions with the structures of the inner ear. Békésy in his germinal work was able to visually observe what he termed the traveling wave in the cochlea of cadavers for high intensity (130 dB SPL) stimuli. He observed that: (1) movement of the stapes caused a traveling wave on the basilar membrane; (2) a stimulus of a given frequency caused vibration of the basilar membrane which grew in amplitude as the wave traveled towards the apex and after a certain point the motion dampened quickly; (3) the BM was tonotopically organized with the high frequencies at the basal end and the low frequencies at the apical end; and, (4) frequency selectivity for a single point on the BM was very poor (as reported in Pickles, 1988).

The passive component, the only one present in a cadaver cochlea, relies on the physical characteristics of the system such as stiffness, mass and damping to affect the vibration of the membrane. The basilar membrane has been shown to be tuned and vibrates according to its characteristic frequency. Thus the basal end of the basilar membrane is tuned to the high frequencies and the tuning becomes lower in frequency as one moves more apically. A wave with a certain frequency grows in amplitude as it moves apically up the cochlea until it has reached its maximum displacement at the place where the cochlea is tuned to that frequency and then rapidly dampens out as illustrated in Figure 1.2b. This can be calculated using the following equation:

$$f_r(x) = \frac{1}{2\pi} \sqrt{\frac{S(x)}{M(x)}} \qquad (1.4)$$

where f_r = resonant frequency, S(x) = stiffness at a distance (x) and M(x) = the mass of the BM at distance (x). The frequency will increase as the length decreases or as the stiffness increases or as the mass decreases. M(x) appears to be relatively constant, $M(x) = M_o$, so the changing stiffness largely determines the resonant frequency.

The traveling wave as described by Békésy (1960) was shown to move from base to apex no matter where the sound source acted upon the cochlea. Calling this the paradoxical wave, he found that by stimulating his cochlear model at the helicotrema the wave still moved from base to apex. This phenomena is due to the difference between the stiffness and mass along the cochlear partition. When a force is applied, motion will always begin in a stiffness-limited system before a mass-limited one. Therefore, motion of the wave will always be from base to apex. This explains why the pitch is the same no matter whether the sound is heard via air or bone conduction (Zwislocki, 1984).

As shown in Figure 1.2(a), the basilar membrane is wider at the apex than it is at the base. The movement of the BM is not stretch-like but rather it tends to bend like a plate. Also the action on the membrane is restored by the elastic force of the system but

only at the local deformation, this is true as long as the wavelength is larger than the width of the BM. The stiffness of the system comes from stiffness of the cochlear partition which includes the BM, organ of Corti and associated structures. The mass of the system comes from the fluids in the scalae. The damping is due to the resistance of the system causing the amplitude of the wave to diminish.

As the wave travels up the cochlea, the stiffness of the partition decreases. As the stiffness diminishes and the compliance increases, the amplitude of the traveling wave must increase to keep the energy constant. As the stiffness of the BM decreases so does the speed of the wave. The speed is greatest near the oval window and diminishes with the increase in distance. This can be calculated using the formula:

$$v = f * \lambda \qquad (1.5)$$

If the frequency (f) is fixed, one initially observes a large wavelength (λ) and hence a large velocity (v). Subsequently, there is a reduction in the wavelength which in turn produces a smaller velocity. As the wave approaches the point on the BM corresponding to its characteristic frequency (CF) or resonant point, the velocity of the wave diminishes even more and the amplitude increases to show a fairly sharply defined maximum (de Boer, 1979; Dallos, 1992). The resistance now increases and the wave travels more and more slowly as it gets closer to the resonant point. If the damping were decreased at this point, the peak of the admittance function would become larger, and the traveling wave would become larger and more sharply tuned. The maximum membrane amplitude, which is illustrated in Figure 1.4(a), is reached slightly basal of the CF point and it is here that the amplitude begins to drop (Zwislocki, 1974). Zwislocki (1984) demonstrated that as the damping of the partition increases the point at which the maximum amplitude is reached becomes further from the CF. Once past the CF, the movement of the partition becomes mass-limited rather than stiffness-limited and rapidly diminishes. The pressure along the BM also drops as the CF becomes closer (Figure 1.4b).

The traveling wave is said to be produced by the interaction of the stiffness of the partition and the mass of the fluids. Resonance of the partition occurs when the stiffness- and mass-limitation are equal in magnitude but opposite in phase and this will occur at different places on the BM due to the stimulus frequency used (Pickles, 1988). When the stiffness is no longer dominant in the partition motion, the wave dies out. Figure 1.4(c) shows that the phase curve becomes flat after the wave dies out and that the rest of the partition moves in the same phase (Zwislocki, 1984). Therefore, once past the resonance point of the partition no wave propagation takes place.

The long-wave model as described above has several shortcomings. de Boer (1991) described these as violating the long-wave assumption by having the response peak of the wavelength the same size as the cross-sectional diameter of the channel. He further stated that the model does not take into account the vertical fluid movements and the fact that the cochlear channel is wider than the width of the BM. These shortcomings may be overcome by the use of two or three dimensional models which allow for the use of the "short-wave" assumption. This assumption allows for the wavelength to be smaller than the height of the channel.

Traveling Wave Delay

The traveling wave is effected by intensity of the stimulus. Ruggero et al. (1992) define traveling wave delay as the time from the arrival of the click at the tympanic membrane until the onset of the vibration of the basilar membrane (a small middle ear component is included), whereas other people include in it the build-up time. To avoid confusion, the term "transport time" will be used to define the time taken for the traveling wave to travel to the point on the BM associated with its characteristic frequency. The build-up time will include only the time needed to reach the maximum amplitude of the BM. As illustrated in Figure 1.5, an increase in intensity of the click stimulus decreases the time

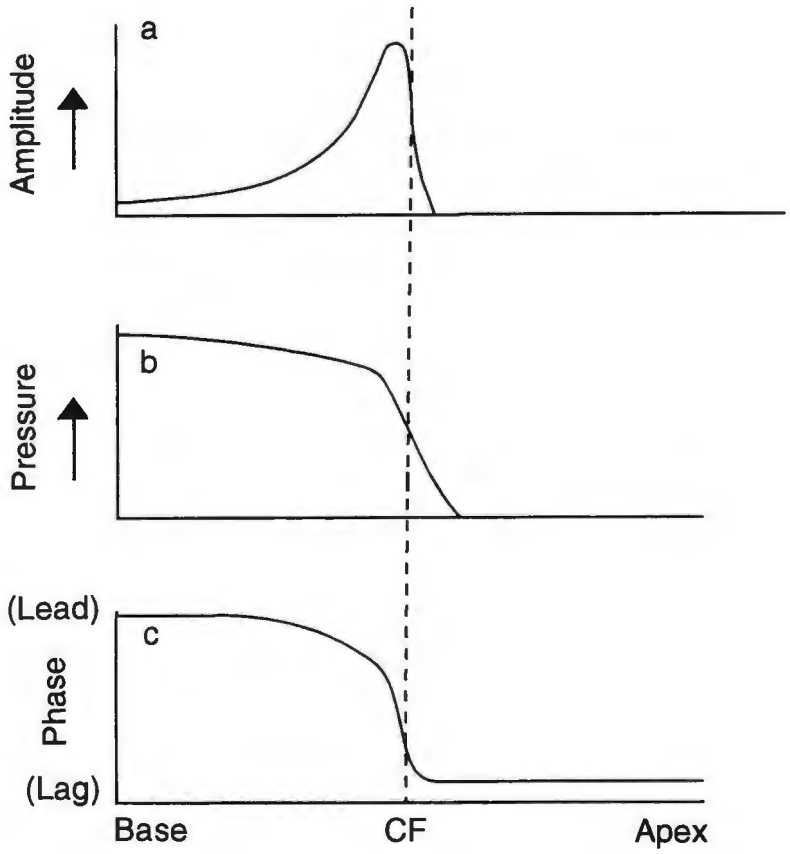


Figure 1.4 Three different aspects of a broadly-tuned, passive mechanical component of the traveling wave at the characteristic frequency. (a) BM displacement has a peak basal to the point of maximum amplitude and a sharp drop on the apical side. (b) The pressure across the BM drops as the CF or resonant point is reached. (c) Changes in phase as the traveling wave moves along the BM (adapted from Pickles, 1988).

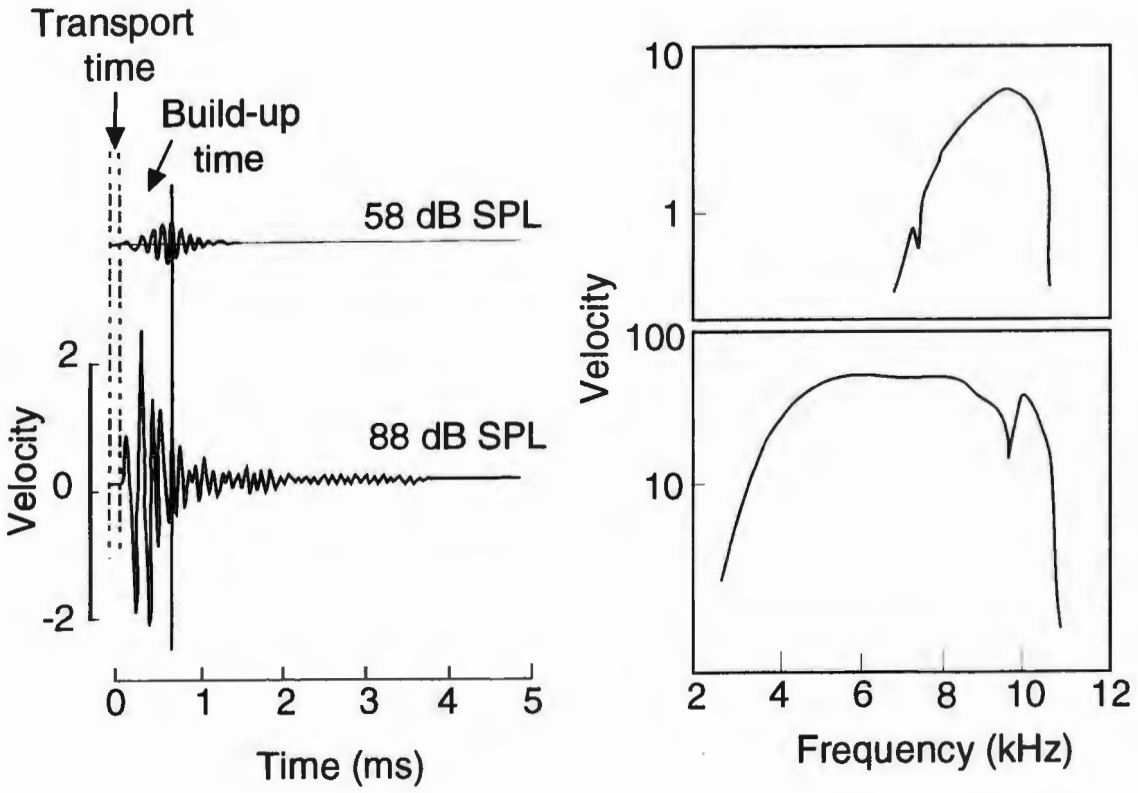


Figure 1.5 Effects of stimulus intensity for a click and its corresponding change in the sharpness of tuning (adapted from Ruggero, 1992). The tuning becomes broader as the intensity of the stimulus is increased. Also note that the maximum amplitude of the more intense click stimuli occurs with a shorter build-up time but that the transport time is the same (adapted from Rugerro, 1992).

to reach maximum amplitude of the BM motion. Ruggero (1994) refers to this measurement as the center of gravity or the weighted-average group delay. He also indicated that the higher intensity stimulation had a more broadly tuned response than did the less intense stimuli.

Therefore, the traveling wave delay or travel time will be impacted by the frequency organization on the BM and the impulse response which is intensity dependent. Different methods have been used to study traveling wave delay or travel time. One method is to use Evoked Otoacoustic Emissions either Transient Evoked Otoacoustic Emission (TEOAE) or Distortion Product Emissions (DPE). TEOAEs are recordings made by stimulating the ear with a click or tone burst and recording the response from the cochlea. DPEs are recordings made by stimulating the ear with two tones and measuring a harmonic or cubic distortion product which is generated in the cochlea and reverse transmitted to the ear canal.

The travel time for an emission, referred to as the round-trip travel time, includes the time from the onset of the stimulus to the recording of the emission. Three hypotheses have been forwarded to help establish the round-trip travel time, and these have been illustrated in Figure 1.6. The first model is the Cochlear-Echo Model which proposes that the round-trip travel time can be interpreted as twice the traveling wave delay (Wit & Ritsma, 1980; Neely et al., 1988). As shown in Figure 1.6(a), this model suggests that the time it takes for a stimulus to travel to the place of generation of the emission is the same time as it takes for the emission to travel from the site of maximum vibration on the BM to the ear canal. However, it implies that the travel time is the time to the maximum of the excitation profile and not the delay that it takes the BM to start moving because this would only be present in the forward traveling wave.

The second model, described by Sutton and Wilson (1983), challenges the cochlear-echo model. They suggested that there would be a transport time to the characteristic place, a build-up time of the activation but that the emission would set up an

acoustic compression wave that would travel back to the ear canal with the speed of sound in water (approximately 1500 m/s) and undergo virtually no delay at all (see Figure 1.6b). Only after the compression wave reaches the stapes will a traveling wave form and propagate to the proper emission frequency place. In this case the long round-trip travel times should be entirely attributable to the traveling wave delay of the stimulus plus a build-up time for the generation of the emission.

The third is the Rutten/Hybrid model suggested by Rutten (1980) and the author (Brown et al., 1994). They state that the round-trip traveling wave delay includes transport time to the BM, a build-up time and a reverse transport time to the ear canal. As illustrated in Figure 1.6(c), there is a distinction made between an intensity independent, asymptotic transmission line part of the transport time and this transport time reflects the frequency-place representation on the BM. The build-up time is the intensity dependent part from the impulse response time of the non-linear BM filter.

Non-linearity of the System

The cochlear build-up time or filter response can be described by the non-linearity of the system filter. Dallos (1988a) stated that nonlinearity means that the amplitude of displacement of the BM grows disproportionally to the increase in sound. The BM response to a sound stimulus is compressive which means that as the stimulus intensity is increased, the BM response grows relatively less. Low level sounds produce the maximum sharpness of tuning and this sharpness is similar to that found in the auditory nerve (Rhode, 1986). High intensity sounds elicit broader responses similar to those found by Békésy in his cadavers. Intensity affects the build-up time but not the transport time. As shown in Figure 1.5, a decrease in stimulus intensity increases the build-up time, however, the transport time remains the same.

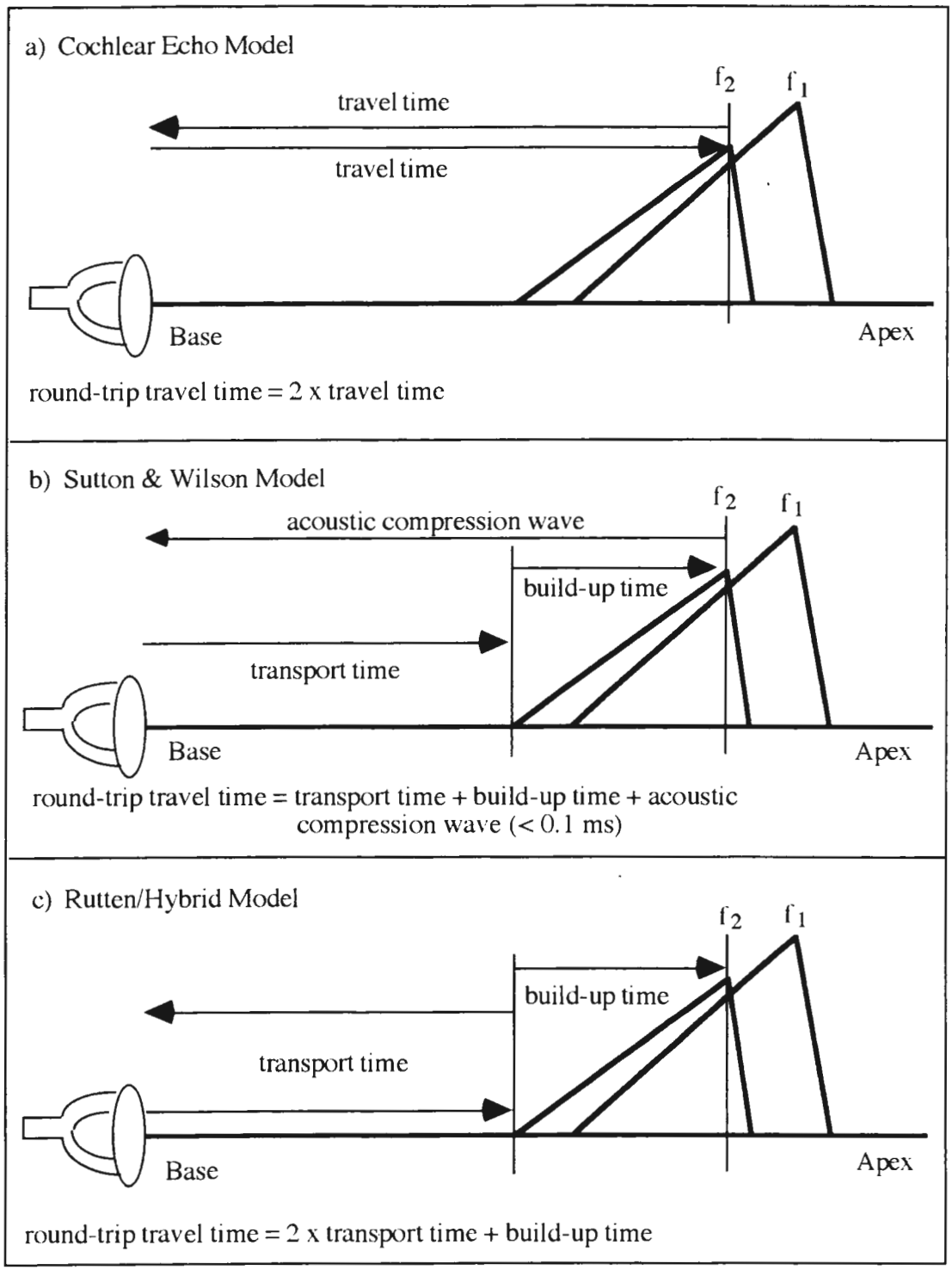


Figure 1.6 Models of round-trip travel times from Otoacoustic Emissions.

Rhode (1971; 1986), using the Mössbauer technique in the squirrel monkey, demonstrated sharp mechanical tuning and nonlinear mechanical vibration in the cochlea. He was able to show that this nonlinearity was only found in the vicinity of the CF and that at higher or lower frequencies, the amount of displacement was proportional to the level of the sound input. The frequency response of the BM has been shown to be susceptible to damage (Khanna & Leonard, 1982). Damage affects the frequency response only in the peak region, the frequency response becomes flat and the peak frequency shifts to a lower frequency.

Active Cochlear Mechanism

The concept of an active process in the cochlea was first proposed by Gold in 1948. He concluded that to account for the high sensitivity, sharp frequency tuning and wide dynamic range observed in VIII nerve recordings, the cochlea must possess a sharply tuned mechanical response system. Gold developed four hypotheses: (1) there should be active elements related to the hair cells; (2) the mechanical observation of the live, healthy cochlea should give a narrow frequency response likely as a result of active positive feedback; (3) on occasion the positive feedback system would become unstable and produce spontaneous emissions, and; (4) that such a system must have a nonlinearity to ensure that the emission would not increase infinitely in size (Norton, 1992). The concept of sharp tuning had been demonstrated previously by Galambos and Davis (1943) whose cochlear nucleus cells recordings revealed sharp threshold response curves. Kiang et al. (1965) also observed that the VIII nerve fibers were much more sharply tuned than those of Békésy's cadaver cochleae.

Kiang et al. (1965) demonstrated that there was a "tuned" response from each VIII nerve fiber when stimulated by a pure tone. They further explained that there is a sharp tip region with a characteristic frequency (CF) to which the unit displays the lowest threshold

and that the sensitivity to frequencies above and below that CF decrease rapidly. Based on these findings the question in these days became, how could the VIII nerve be so sharply tuned if the cochlea is broadly tuned? Johnstone and Boyle (1967) and Rhode (1971) used Mössbauer measurements of BM motion to show that BM motion was more sharply tuned than Békésy had indicated. Using combination tones to generate $2f_1$-f_2 distortion products Goldstein and Kiang (1968) found that responses from the auditory nerve paralleled those of psychophysical experiments. They suggested that this nonlinear mechanism that generates the response must be located in the cochlea. Kiang et al. (1970) presented further evidence by showing that in the presence of healthy, normal functioning OHC the BM is sharply tuned and nonlinear. In the absence of OHC, behavioural thresholds are approximately 40-60 dB poorer (Ryan & Dallos, 1975) and the shape of the tuning curves was different than normal, i.e. very broad tuning or highly elevated thresholds at CF (Dallos & Harris, 1978). Recently, it has been shown that IHC can be selectively destroyed by carboplatinum (Takeno et al., 1994). After treatment with this ototoxic drug, cochlear action potential thresholds were elevated in proportion to the IHC damage but cochlear microphonic thresholds were close to normal which corresponded to the preservation of OHC.

Békésy, as reported earlier, demonstrated that the BM is broadly tuned and suggested that the auditory nerve must provide the extra tuning required. However, data from Johnstone et al. (1986) showed that the SPL needed to produce a given velocity of the BM is much larger when OHCs are damaged. Therefore, the concept of active cochlear mechanics which allows more sensitive vibration of the BM and feedback of mechanical energy into the motion has become important.

During the active process the vibration of the BM is enhanced by energy provided somehow in the organ of Corti. For stimulus intensities below about 70 dB, the cochlear amplifier provides additional energy to the system which in turn enhances the vibration of a

narrow segment of the BM near the apical foot of the traveling wave envelope. Davis (1983) indicated that the cochlear amplifier increased the sensitivity of the system by about 45 dB in the mid frequency region. This active process or cochlear amplifier needs metabolic energy, which is the reason it was not observed in cadavers or by those doing postmortem animal experiments. This active component is sensitive, and metabolically vulnerable to ototoxicity (e.g. aspirin), vulnerable to mechanical insult (e.g. noise exposure, anoxia) (Johnstone et al., 1986) and dependent upon the integrity of the outer hair cells (Ryan & Dallos, 1975). The impact of the active mechanism increases rapidly (e.g. with a slope >1) with stimulus intensity, this is to say that the active, low-level cochlear amplifier is highly nonlinear (Rhode, 1971; 1986).

The nonlinearity of the system is only seen around the CF because this is where the active process takes place (Davis, 1983). At frequencies which are much higher and lower than the CF, the displacement is proportional to the level of the sound and the system behaves linearly. The operating range of this process is between 0 and 45 dB SPL and the maximum sharpness of tuning occurs at these low sound pressure levels. This is because the nonlinearity of the response at high intensities will saturate as the linear passive component becomes larger than the active process. The traveling wave behaves nonlinearly near its peak or tip, and is activated just basal to the CF as shown in Figure 1.7. The development of the active process begins approximately at a CF one half octave below the frequency of the stimulus to produce the sharp tuning at the CF.

Source of Energy for Active Process

An active process by definition means that it is adding energy into the system but where is that energy coming from? The current theory is a motor theory which is based on the motor action of the OHCs and how they intensify the motion of the BM which is the stimulus for the IHCs (Dallos & Martin, 1994). This theory has developed from recent

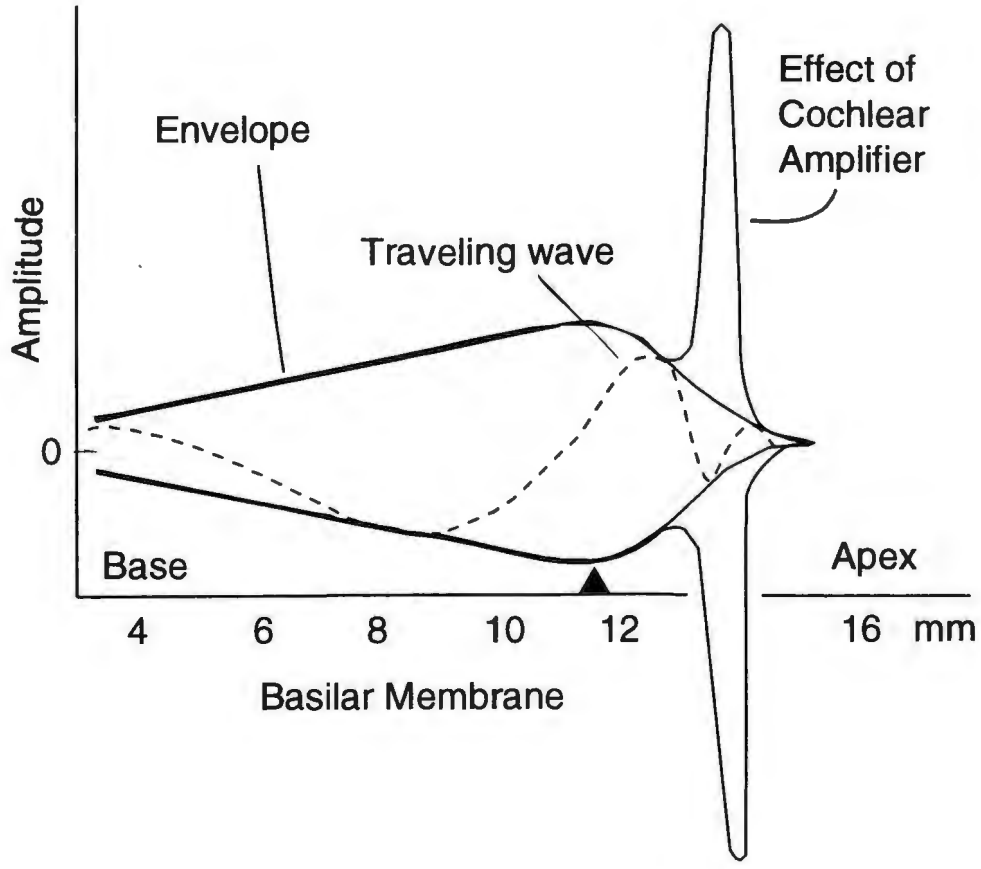


Figure 1.7 A traveling wave and the effect of Davis' cochlear amplifier. The peak of the traveling wave envelope occurs approximately one octave below (or 2-3 mm closer to the stapes as indicated by the ▲) the CF of the stimulus (adapted from Davis, 1983).

research which has shown that the OHCs are capable of acting as both motor and sensory units. Brownell et al. (1985) have shown that OHCs are capable of making a contractile motion, they shorten or lengthen when stimulated by depolarizing or hyperpolarizing currents. This ability to change length in response to an intracellular voltage change means that they can increase the distance between the reticular lamina and the BM. This could in turn provide the active mechanical process to amplify the weak vibrations sufficiently to stimulate the IHCs.

Dallos (1992) states that normal cochlear function is dependent on an active, mechanical feedback process and the OHCs are the agents for the feedback. This process is also referred to as "negative damping" which means that in addition to energy being dissipated by frictional (viscous) resistance, energy is added to the traveling wave as it traverses this segment of the BM (Davis, 1983). Neely and Kim (1983) have suggested that the cilia of the OHC are the possible site of this energy release. There are three reasons why the OHC have been suggested as the site of this energy: (1) OHC operate in conjunction with the basilar and tectorial membranes; (2) despite IHC having most of the afferent sensory innervation, elimination of OHC causes broad tuning and significant hearing loss (Kiang et al., 1970; Dallos, 1992), and; (3) most of the efferent fibers connect to the OHC suggesting a motor function and stimulation of them changes the IHC response.

Interfering with OHC function profoundly affects the active mechanical process. OHC function as biomechanical force generators by amplifying BM motion through a feedback loop (Ruggero, 1992). This is possible because the OHC are both mechanoelectrical transducers and electromechanical transducers. This dual sensor-effector operation of the OHC is the apparent basis of the amplification of the passive traveling wave by the active feedback. OHC have been shown to change shape and this shape change can alter micromechanical processes. Their displacement affects the traveling wave-

induced deformation of the organ of Corti, feeding back energy so that the resulting traveling wave is amplified. The absence of the cochlear amplifier within the auditory system results in elevated thresholds and broad tuning with the CF of a given cochlear place shifted downward by one-half to one octave.

The results of this active process can be seen in tuning curves, auditory thresholds and otoacoustic emissions. A tuning curve is divided into two parts, the tip and the tail. The tip of a neural tuning curve corresponds to a narrow segment of the BM which has enhanced vibration. The tail of the tuning curve corresponds to the classical envelope of the traveling wave. It has been reported that the tip portion which corresponds to the cochlear amplifier is vulnerable to physiologic damage such as noise exposure or anoxia. Movement of the BM by the traveling wave is amplified by the cochlear amplifier at low levels. At moderate levels it is only slightly modified and it is protectively restrained at high intensities that would otherwise be injurious to the ciliary mechanisms.

Emissions Consequence of Active Processes

One of Gold's (1948) hypotheses was that there would be occasions when the positive feedback system would be unstable and produce a clear note that could actually be heard. The idea that sound energy could be reverse transmitted from the inner ear into the ear canal was novel in Gold's day but now this reverse energy flow can be recorded from the ear canal. Kim et al. (1980) reported that they were able to record and model distortion signals which propagated from the cochlear region of the f_1 and f_2 components both apically to the CF place for the distortion and basally toward the stapes, through the middle ear and into the ear canal. Hubbard and Mountain (1983; 1990) demonstrated this reverse transduction by injecting ac current into the intact cochlea and measuring an electrically-evoked acoustic emission at the eardrum. Matthews (1983) modeled this reverse transmission of a signal from the cochlea of a cat and found that the properties of the circuit

model were highly frequency dependent. He also reported that different distortion products could be measured in the ear canal of the same animal by different delivery systems because they "load" the auditory system differently. This cochlear "loading" is important as it can even effect the distortion propagation within the cochlea.

OTOACOUSTIC EMISSIONS

In 1978, Kemp first described the phenomenon of the otoacoustic emissions (OAE). In this germinal work, he demonstrated that the cochlea does not only receive sounds but also produces acoustic energy which can be recorded in the ear canal. Typically the human ear is not thought of as a sound-producing organ, however, it is precisely that which makes it possible to study the mechanical aspects of cochlear function in humans (Zurek, 1981). Initially OAEs were called the "Kemp echo" and were received with much skepticism, however currently it is indeed an accepted phenomenon and not just an artifact as previously believed (Wilson, 1984). OAEs are defined as sounds which are produced by the cochlea and can be recorded in the ear canal. The sounds are from the cochlea where they are generated by active mechanisms which amplify the sounds to produce a pattern of vibration which is then reverse transmitted through the middle ear to the ear canal (Probst, 1990). These resulting pressure changes can be picked up for analysis by a microphone placed in the ear canal and are commonly referred to as emissions.

These emissions are divided into two classes: Spontaneous Otoacoustic Emissions (SOAE) and Evoked Otoacoustic Emissions (EOAE). The difference between the two classes can be found in their method of generation. The first class, SOAE, does not require an external stimulus to produce an emission. The second class, EOAE, requires a stimulus to produce the emission. Kemp (1988) reported that OAE could be used to non-invasively and objectively study the mechanical aspects of cochlear function. Previously, evoked potentials which rely on the nerve's response were used to study the cochlea.

Spontaneous Otoacoustic Emissions

SOAEs are narrow-band signals which may be present in the ear canal in the absence of an external stimulus (Zurek, 1981; Probst, 1990; Zwicker, 1990). Many researchers agree that these tonal acoustic signals are generated in the cochlea (Schloth, 1983; Cianfrone & Mattia, 1986; Mott et al., 1989; Norton et al., 1989; Probst, 1990; Glattke & Kujawa, 1991) and some suggest that they originate as spontaneous and continuous vibrations in the cochlea (Zurek, 1981). Schloth (1983) indicated that SOAEs were probably related to the mechanisms whose function increases hearing sensitivity. These emissions are present for long periods of time with little change in frequency but a greater change in amplitude.

SOAEs are very strong, often greater than 0 dB SPL, but they are generally inaudible to the subject (Zurek, 1981; Schloth, 1983; Cianfrone et al., 1990; Lind & Randa, 1990). Originally, these emissions were thought to be 'objective tinnitus', which has been described in the literature for many years. However, in only a small percentage of patients can their tinnitus be linked to a SOAE (Tyler & Conrad-Armes, 1982; Bonfils, 1989; Norton et al., 1990). Some subjects report hearing beats or roughness when low level external tones near their SOAE frequency are presented (Evans et al., 1981; Norton et al., 1989). SOAEs are observed frequently and are easily measured in individual's with normal hearing but they do not appear in frequency regions with a hearing loss (Bonfils, 1989; Lind & Randa, 1990; 1992). Emissions have been shown to disappear after a fatiguing stimulus of sufficient energy and duration has been presented to the ear (i.e. a Temporary Threshold Shift) but over time will gradually return to their original amplitude (Fritze & Köhler, 1986; Norton et al., 1989).

The frequency range for a SOAE is between 0.5 and 9 kHz as shown in Table I.1. In this range an individual may have one or several emissions. However, the largest number of SOAEs are found between 1 and 2 kHz (Zurek, 1981; Schloth, 1983; Cianfrone

Investigators	Subjects with Emissions (%)	SOAE frequency (Hz)	SOAE amplitude (dB SPL)	Multiple emissions (%)	Bilateral Emissions (% of subjects)
Zurek (1981)	50	960 -7705	-6.0 - 17.5	22% of subjects	19.0
Tyler & Conrad-Armes (1982)	25	800 - 2000	2.0 - 12.0		
Fritze (1983)	29	<1000 - >6000	-2.0 - 18.0	14% of ears	39.0
Schloth (1983)	33.6% of ears	775 - 3990	< 15.0	21.9% of ears	
Rabinowitz & Widen (1984)	42% of ears	1000 - 7700	< 15.0		
Strickland et al. (1985)	Children - 40 Infants - 38	862.5 - 7057.0 1634.5 - 4231.2*	-1.6 - 29.3 10.0 - 30.4	55% of subjects 63% of subjects	50.0 25.0
Bright & Glattke (1986)	43	527 - 5440	-11.0 - 19.0	66% of ears	30.6
Cianfrone & Mattia (1986)	30.8	1000 - 2600	3.0 - 20.0	29.6% of ears	68.8
Probst et al. (1986)	43 % of ears		-5.0 - 10.0	67% of ears	
Frick & Matthies (1988)	25.8-38.7	1304 - 4666	1.2 - 15.4	62.5 - 66.7% of subjects	33.3
Zizz & Glattke (1988)	41.0	662 - 3407	-10.0 - 18.9	23% of subjects	15.0
Bonfils (1989)	35.05	500 - 7000			20.68
Lind & Randa (1990)	71.7	648 - 9360	1.0 - 26.5	46.2% of ears	31.6
Lonsbury-Martin et al. (1990b)	60	800 - 7000	-17.0 - 15.0	86% of ears	60.0
Bonfils et al. (1992)	61			68	40
Burns et al. (1992)	infants - 64 adults - 62	2500 - 5000 1000 - 2000	mean 8.5 mean -2.6	49 42	37 34
Kok et al. (1993)	Infants - 77.8	1000 - 6000	-2 - 42	(on average 5.5/ear)	67.4

*difficult to measure below 2000 Hz because of noise floor with infants.

Table I.1 Incidence of SOAEs in normal ears.

& Mattia, 1986). This is probably due to the effectiveness of the retrograde transfer of the middle ear in this frequency range (Kemp, 1980; Probst, 1990). The frequency of a SOAE although remarkably stable over time, does have some variability. In addition, the spectral profile of the emission frequency is always very sharp and the overall spectral shape of the SOAE is constant over time (Cianfrone & Mattia, 1986). The range of amplitudes for an SOAE, as shown in Table I.1, was between -17 and 30 dB SPL. The high-level emissions are considered to be the exception and in general amplitudes do not exceed 20 dB SPL. The lower value will depend heavily on the level of the noise floor in which the emission was recorded. The amplitude of the SOAE, unlike it's frequency, is relatively unstable (Cianfrone & Mattia, 1986).

Incidence of SOAEs

Spontaneous Otoacoustic Emissions have been studied since 1979 and there are a number of studies which have investigated the incidence of SOAEs in normal hearing individuals (Table I.1). Although there is not a definitive answer to the question of incidence, the results indicate that approximately 40% of normal hearing individuals have at least one SOAE. Even though 40% have SOAEs, it is not possible to predict if an individual will have a SOAE, what frequency it will be found at, if an ear will have more than one or even if they have one emission in one ear whether they will have an emission in the other ear (Bright & Glattke, 1986). A healthy inner ear is required for an emission to be present. Individuals with SOAEs will usually have behavioural thresholds better than 15-30 dB HL (Bright & Glattke, 1986; Bonfils, 1989).

Emissions have been shown to occur at more than one frequency in the majority of ears that have emissions (Bright & Glattke, 1986). The number of multiple emissions in a single ear ranges from a minimum of 2 to as many as 19 (Lind & Randa, 1990). Table I.1 shows that there is a wide range in the number of subjects with multiple emissions.

Multiple emissions occur in anywhere from 15 to 80% of ears with emissions. The incidence of bilateral emissions, as shown in Table I.1, is between 20 and 70% of the subjects tested. Due to this large variation in the incidence of bilateral emissions, the probability of having a SOAE in one ear does not appear to be affected by the presence of an emission in the individual's other ear (Wier et al., 1984).

The discrepancies among results found in Table I.1 are most likely due to differences in the criteria used for assessing the presence of a SOAE. The recording equipment and techniques were also different which might lead to a better (or worse) noise floor or frequency response. Variation may also be due to the definition of what makes an emission. Some investigators consider an emission to be present if it is 2.0 dB above the noise floor (Frick & Matthies, 1988) and others use as much as 5.0 dB difference between the noise floor and the peak (Strickland et al., 1985) before saying that an emission is present. Schloth (1983) reported that a certain minimal frequency separation between neighbouring emissions is required for multiple emissions. If several emissions were recorded from one ear, the emissions would be separated by at least 100 Hz.

The age of the subject has been shown to have some effect on the incidence of SOAEs. Bonfils (1989) revealed that the percentage of ears with SOAEs decreased with increasing age (years). The greatest significance is that there were no recordable SOAEs in subjects over 70 years of age. However, there was no significant difference in the number of emissions per ear between the different age groups. Strickland et al. (1985) studied the incidence of SOAEs in children and infants and found that 40% of the children (mean age = 9 years) and 38% of the infants (mean age 30 days) had a SOAE. This was within the range for adults, therefore no significant difference was found in the incidence of SOAE when comparing infants and children with the adult population. Others (Bargones & Burns, 1988; Bonfils et al., 1992; Burns et al., 1994) found that the incidence of SOAEs in healthy preterm and term-born infants was similar but that the frequency and amplitude of

SOAEs were higher than those of adults. A longitudinal study of infants from 1 to 24 months revealed that SOAE amplitude decreased with age and the largest decrease in amplitude was in the high frequencies (Burns et al., 1994). Although there was a change in amplitude of the SOAE, the frequency did not shift significantly suggesting that these developmental changes were probably attributable to the changes in the external and middle ear.

Amplitude and Frequency Changes in SOAEs

The stability of a SOAE has been questioned in a number of studies (Zurek, 1981; Schloth, 1983; Burns et al., 1984; Wier et al., 1984; Cianfrone & Mattia, 1986; Lind & Randa, 1992) Over time drifts in frequency and shifts in amplitude have been reported. The fluctuations in amplitude (< 5 dB) and frequency (2-10 Hz) are relatively small when compared to the amplitude or frequency of the emission itself (Wier et al., 1984; Dijk & Wit, 1990). However, the more intense SOAEs often exhibit substantial short-term, spontaneous instabilities in both amplitude and frequency (Rabinowitz & Widin, 1984). Drifts in frequency and shifts in amplitude have been seen in both the short i.e. within seconds (Lind & Randa, 1990) and long-term i.e. 30 minutes or more (Schloth, 1983).

In looking at the short term, Lind and Randa (1990) found that there was a small (0.96 Hz) mean difference in emission frequencies between the first and second measurements. In addition, there was no frequency region which was more prone to frequency shifts than any other. Amplitude shifts were larger in the lower frequencies, however, for frequencies above 2 kHz differences of less than 0.5 dB were found. These differences may have been due a change in the noise floor which decreases the absolute amplitude greater than the relative amplitude, which might not change at all.

SOAE frequencies and amplitudes have been shown to fluctuate in the long-term. Ruggero et al. (1983) reported a frequency drift of 10 Hz over a 30 minute time period.

Frick and Matthies (1988) also found a small frequency drift of between 4 and 12 Hz and a < 4.1 dB shift in amplitude within a one hour time period. The drifts and shifts were not caused by changes in the physical characteristics of the microphone or the probe's interaction with the ear, to changes in middle ear transmission properties or to changes in temperature (Wit, 1985; Whitehead et al., 1989).

Evoked Otoacoustic Emissions

Evoked Otoacoustic Emissions (EOAE) are the second of the two classes of otoacoustic emissions. This class of OAEs differs from the first class, SOAE, in its method of generation. EOAEs are evoked by using different types of acoustic stimuli and can be divided into groups according to the type of stimuli used. There are three different types of EOAEs, each using a different type of stimuli to produce the emission. The different types of EOAEs are: (1) Transient Evoked Otoacoustic Emissions (TEOAE); (2) Stimulus Frequency Otoacoustic Emissions (SFOAE), and; (3) Distortion Product Emissions (DPE).

EOAEs can be recorded in the ear canal and by definition are sounds which come from the cochlea. Support for this idea comes from Kemp and others who have shown that EOAEs are not neural responses by reversing the polarity of the stimulus and having the TEOAEs polarity reverse (Kemp & Chum, 1980) or showing that OAEs are not affected by stimulus rates (Kemp, 1982), or sectioning the VIII nerve (Siegel & Kim, 1982) or efferent system (Siegel & Kim, 1984) and still being able to record emissions. This indicates that the response is pre-neural and independent of both afferent and efferent innervation. However, OAE amplitude can be deminished by either electrical stimulation at the crossed olivary complex bundle (Mountain, 1980) or in the form of noise presented to the opposite ear (Collet et al., 1990a; Puel & Rebillard, 1990; Veuillet et al., 1991). Other evidence of a cochlear location for the mechanism responsible for the emission is: (1) the latency of the

emission is frequency dependent (Norton & Neely, 1987; Neely et al., 1988); (2) OAEs are not found in ears with a moderate to profound sensorineural hearing loss; (3) particular frequency components within the OAE can be suppressed by other stimuli making for sharp tuning, and; (4) OAEs are physiologically vulnerable to anoxia, noise exposure or ototoxicity (Kim et al., 1980; Johnsen & Elberling, 1982a).

Transient Evoked Otoacoustic Emissions

TEOAEs are called transient because the responses are elicited by the use of brief acoustic stimuli such as clicks or tone bursts. These rectangular or Gaussian-shaped clicks or tone bursts are repeatedly presented to the ear. The microphone records the output which is then high-pass filtered (at approximately 0.3-0.5 kHz) and averaged by time-locking it to the stimulus. Usually there is some artifact rejection system either eliminating the response above a preselected noise level or by adaptive strategies that manipulate subaverages following linear cancellation. This averaged waveform is fast Fourier Transformed (FFT) and then tested for reproducibility by cross-correlation techniques (Probst et al., 1990; DeVries & Decker, 1992). The frequency spectrum of TEOAEs has been suggested by Kemp et al. (1986) to reflect the middle ear transfer function, which is most efficient in the 1 to 1.5 kHz range resulting in a transmission loss of about 12 dB/octave for frequencies higher and lower than this range.

Input/output (I/O) functions were first reported by Kemp in 1978 when he reported that there was a near linear growth up to about 13 dB HL and then a strong saturation for any higher levels of stimulation (Probst et al., 1991). Other investigators (Wit & Ritsma, 1979; Wilson, 1980a; Johnsen & Elberling, 1982a & b) found that there was a constant growth of TEOAEs below, and a pronounced saturation above, a 10-20 dB HL stimulus level. Probst et al. (1991) reported a general consensus that TEOAE growth is nonlinear

for stimuli > 20-30 dB SL. The most distinctive feature of a TEOAE is the saturation with increasing stimulus level which can be used to identify these emissions (Probst, 1990).

Stimulus-Frequency Otoacoustic Emissions

SFOAEs utilize a stimulus consisting of a pure tone that is swept relatively slowly over a specific frequency range and the response is measured from the ear canal with a narrow filtering device. The emissions are evoked by manipulating either the frequency or the level of the stimulus. As the stimulus is swept across the frequencies, it creates an interaction which is dependent on the phase relationship between the input and the output signal. This results in frequency regions with enhanced acoustic energy next to regions with reduced levels which are recorded as peaks and valleys (Probst et al., 1990; DeVries & Decker, 1992). In order to separate the response from the stimulus, either a multilevel or suppression technique is used.

A variety of results have been reported for input/output functions for SFOAEs. Although there is a strong saturation to moderate stimulus levels, different shapes of the entire I/O function have been reported (Probst, 1990). Dallmayr (1987) and others (Probst, 1990) reported that at low stimulus levels (<20 dB above threshold) SFOAEs grow linearly with the stimulus but above this level they grow very little, similar to the TEOAE. Some investigators (as reported by Probst, 1990) have noted different functions for frequencies where a SOAE is present as compared to those without a SOAE present.

Distortion Product Emissions

EOAEs can also be evoked using two tones as the stimuli. If the cochlea is stimulated by two-tones simultaneously at frequencies f_1 and f_2 ($f_2 > f_1$), additional tones or harmonics may be produced such as the cubic distortion product, $2f_1-f_2$ (Goldstein & Kiang, 1968). Distortion Product Emissions (DPEs) represent evoked nonlinear responses

because they consist of new frequencies that are not present in the eliciting stimuli. The frequency of the cubic distortion product is related to the frequencies of the two primary tones used as the primary stimuli by a simple algebraic expression, the most common of which is $2f_1$-f_2. This cubic distortion product is reverse transmitted from the cochlea through the middle ear and is recorded in the ear canal as the DPE.

The $2f_1$-f_2 DPE is generated in the frequency region of the basilar membrane (BM) corresponding to the interaction or overlap of the stimulus tones i.e. f_1 and f_2 (Kim et al., 1980; Kemp & Brown, 1984; Furst et al., 1988). The region of the cochlea corresponding to the interaction of the two primaries is illustrated in Figure 1.8. Kemp and Brown (1984) found that suppressors in the vicinity of the primaries and not at the DPE frequency had the greatest effect. If the location of the primary tone has been damaged by noise induced threshold shifts, then DPEs are either reduced or eliminated (Lonsbury-Martin et al., 1987). Studies of different order distortion products (i.e. $2f_1$-f_2, $3f_1$-$2f_2$ & $4f_1$-$3f_2$) using the f1-sweep technique revealed similar group mean delays across DPE order (Brown et al., 1992; Stover et al., 1994). This suggests a common place of origin for all order DPEs.

The site which makes the most significant contribution to the generation of the DPE is at this time controversial. A review of the literature described two possible locations, the f_2 place (Brown & Kemp, 1984; Fahey & Allen, 1986; Matthews & Molnar, 1986; Furst et al., 1988; Brown & Gaskill, 1990; Brown et al., 1992; Kimberley et al., 1993) or the geometric mean of f_1 and f_2 (Martin et al., 1987; Lonsbury-Martin et al., 1991a; Whitehead et al., 1994b; Popelka et al., 1995). The geometric mean of the primary-tone frequencies is calculated using $(f_1 * f_2)^{0.5}$. For example, if f_1 = 1 and f_2 = 1.2 kHz, then the geometric mean would equal 1.095 Hz and if f_1 = 10 and f_2 = 12 kHz, then the geometric mean would equal 10.955 kHz. The difference between the geometric mean and the f_2 place is 0.1 and 1.046 kHz respectively. This difference is small especially when compared to the typical frequency range of DPE testing (e.g. 1 to 10 kHz).

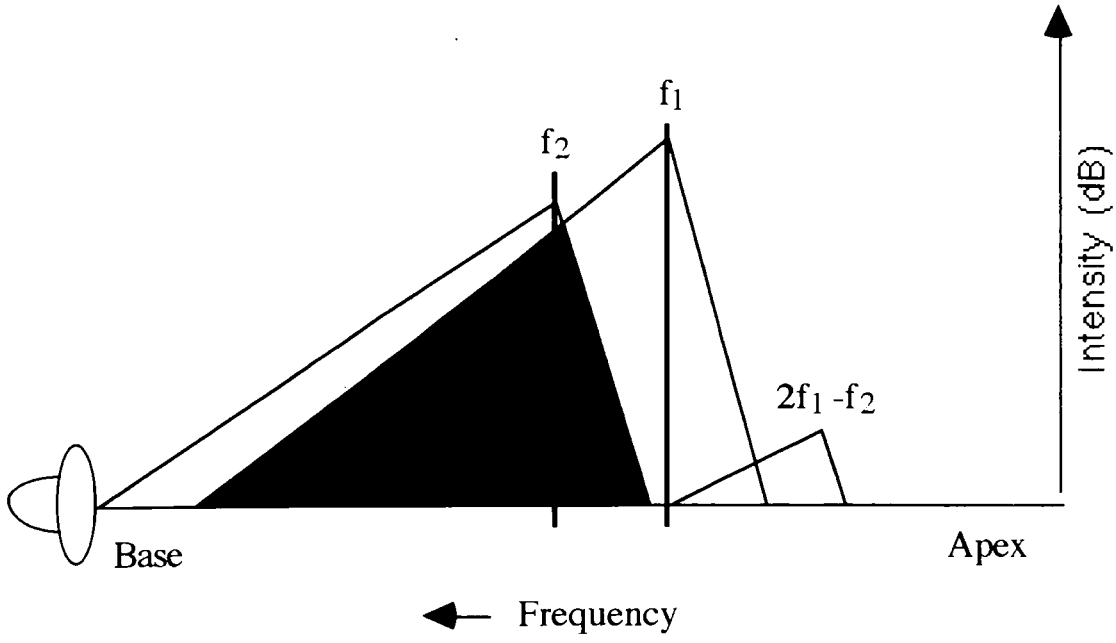


Figure 1.8 Schematic of a traveling wave on the BM for the primary tones, f_1 and f_2 and the corresponding distortion product, $2f_1$-f_2. Note the over lap area of the primary tones and the proximity to the f_2 tone (adapted from Lonsbury-Martin & Martin, 1990).

The use of f_2 or the geometric mean of the primaries to compare with the frequency of the behavioural threshold will be of little consequence when testing an ear with normal hearing. This is because the primaries reach maximum BM displacement over a small range. DPEs are detectable at frequency regions where hearing is normal. Emissions are not present to low-level stimuli when behavioural hearing threshold levels are above 15-20 dB (Gaskill & Brown, 1993). DPEs are typically reported as either: (1) a "DP audiogram" which is done by holding the intensity of the primary tones constant and sweeping across the frequency range where the DPE amplitude is plotted as a function of the stimulation or f_2 frequency (Lonsbury-Martin & Martin, 1990); or (2) a "DPE Growth curve" (or input/output function) which holds the frequency constant and increases the intensity of the primary tones (Nelson & Kimberley, 1992).

Effect of Age

When using DPEs to distinguish individuals with normal hearing from those with hearing losses, one must determine what is a normal emission. There are variables which can effect the emission especially in terms of its amplitude which need to be considered in order to make this determination. The absolute amplitude of the emission depends on stimulus recording parameters (Gaskill & Brown, 1990) and hearing threshold (Nelson & Kimberley, 1992). Other investigations (Lafreniere et al., 1991; Brown et al., 1994) have reported that age of the subject also influences absolute amplitude of the emission. There have been only a few studies which have focused on the effects of aging on emissions and they have shown that when age increases, the threshold increases and the incidence and frequency range decrease (Bonfils et al., 1988; Collet et al., 1990b). Studies using EOAEs in newborns found that not only were they able to test infants but that 80% (Stevens et al., 1991) to 95% (Dolhen et al., 1991) had emissions and that these emissions were generally larger than those of adults (Kemp, 1989).

Presbycusis has been suggested as the cause for a decrease in the occurrence and an increase in threshold which was related to a decrease in hearing sensitivity with age (Bonfils et al., 1988). All subjects tested in his study from 2 to 60 years of age had TEOAEs but as age increased only 35% of the subjects had them. Threshold also varied with age, it was constant until 40 years of age but after this age it increased linearly. Collet et al. (1990b) in his replication study also found that the incidence decreased after age 60. They noted a difference in both the EOAE and the subjective thresholds according to age, as age increased there was an increase in both the emission and subjective thresholds. However the decrease in TEOAE incidence in the over 60 group may have been caused by hearing loss and not by age alone (Probst, 1990).

The influence of the aging process on 30 to 60 year olds was investigated by Lonsbury-Martin et al. (1991a) who reported that DPE amplitude decreased and detection threshold increased with age. Audiometric testing confirmed previous findings in that auditory acuity decreases with age and increasing frequency of the test stimuli. The results from the "DP audiogram" or from Input/Output functions showed that the oldest ears tended to generate the smallest DPEs especially in the higher frequencies. Differences in absolute amplitude have been noted, especially when comparing infant data to adult data (Lafreniere et al., 1991; Brown et al., 1994). Whitehead et al.(1994b) has reported that DPEs are approximately 3 dB greater in amplitude in infants than in adults.

Effect of Hearing Loss

The effects of hearing loss on EOAEs has been studied by many researchers since EOAEs have been suggested as a possible hearing screening tool. Kemp (1978) was the first to study the effects of sensorineural hearing loss on TEOAE. He reported that TEOAEs were not found in ears with a >30 dB hearing loss. Further investigations were in general agreement, revealing that as the threshold of hearing increases, TEOAEs rapidly

reduce in amplitude until they become undetectable when the loss exceeds a certain value. The value above which the TEOAE disappears varies from study to study. These values included 15-20 dB (Kemp et al., 1986, Kemp, 1989); 25 dB HL (Lutman, 1989); > 30 dB HL (Harris & Probst, 1991); > 35 dB HL (Bonfils et al., 1988; Bonfils & Uziel, 1989; Robinette, 1992) to as much as > 40 dB HL (Collet et al., 1989).

Probst (1990) reviewed a number of studies which addressed TEOAEs and hearing loss. He concluded that TEOAEs can be present in ears which have some preservation of hearing at specific frequencies along with a marked sensorineural hearing loss at other frequencies. TEOAEs were found from 0.5 to 6 kHz, however, the most common frequency range was from 1 to 4 kHz (Robinette, 1992). This study found good specificity for high-frequency hearing loss but poor frequency specificity for low frequency (< 2 kHz).

DPEs and the effects of hearing loss have also been studied. DPEs were reduced in amplitude or absent in ears with hearing loss (Leonard et al., 1990). Kemp et al. (1986) found that in ears with high frequency hearing loss, the DPE amplitudes were significantly smaller than normal at the frequencies associated with the loss. Even though the ears had a mild loss (<30 dB HL) the DPEs were still present. DPEs were always present in ears, if the thresholds at predominant frequencies were better than 20 dB HL. However, emissions were absent or attenuated if behavioral thresholds exceeded 50 dB HL (Harris, 1990). Kimberley and Nelson (1989) found that DPE measurements could predict frequency specific auditory thresholds to within 10 dB over a range of sensory thresholds from 0 dB SPL to 60 dB SPL. Other investigators (Probst & Hauser, 1990; Smurzynski et al., 1990; Nelson & Kimberley, 1992) reported that DPE amplitudes were related to the general shapes of the audiogram and that DPEs were detected at frequencies where hearing loss was normal and that DPEs were reduced when the primary frequencies f_1 and f_2 corresponded to the region of hearing loss.

External/Middle Ear Effects

Different types of hearing loss (i.e. conductive) can affect the EOAE. Conductive losses greatly reduce the amplitude of the emission (TEOAE or DPE). In this type of loss, the intensity of the stimulus and that of the emission were both reduced thus restricting the interpretation of the results (Zurek et al., 1982; Kemp, 1986; Collet et al., 1989; Lutman, 1989; Leonard et al., 1990). In order to record an emission the stimulus must pass through the middle ear during the forward transmission of the stimuli to the cochlea and then again as the emission is reverse transmitted to the ear canal. Brown et al. (1995) suggested that middle ear effusion would seriously affect the level of the emission and that with low level stimuli infants with fluid would not have DPEs.

The external ear canal in newborns has been shown to contain vernix. This debris in the canal was shown to decrease the emission. However if it is removed, the number of ears passing the TEOAE test increased (Chang et al., 1993). Pressure in the ear canal used to equalize the middle ear pressure was studied in children and adults (Naeve et al., 1992; Osterhammel et al., 1993; Trine et al.; 1993). They revealed that positive or negative pressures reduced the emission by 3-6 dB and equalization of the middle ear pressure would increase the amplitude of the emission. The influence of pressure change is frequency specific with low frequency emissions being more affected than high frequency emissions (Kemp et al., 1990; Hauser et al., 1993; Osterhammel et al., 1993). Kemp and colleagues (1990) suggested that fluid in the middle ear would cause loading of the tympanic membrane and ossicles and prevent the recording of emissions.

Amplitude effects

The DPE is characterized by a frequency, amplitude and phase value and these values change according to the stimulus parameters set by the investigator. Changes in intensity or frequency of the stimulating tones have a corresponding effect on the

amplitude, frequency and phase of the DPE. Other important stimulus parameters required to create the optimal DPE are the ratio (f_1/f_2) of the primaries, the level difference between the primary tones and the intensity level of the primaries (Schmiedt, 1986a; Probst et al., 1990). These stimulus parameters will affect the amplitude of the resulting emission that is recorded in the ear canal. The two primaries are mixed acoustically in the ear canal and it is the nonlinear properties of the cochlea that are responsible for generating the distortion. The emission is amplified, averaged, analyzed and displayed as a function of either the geometric mean or f_2. This is an objective test, requiring no participation by the subject. However, the background noise either from the surrounding area or the subject themselves can affect the amplitude of the emission.

The level of the stimuli influences the amplitude of the DPE emission in normal hearing individuals. Using input/output functions or growth curves, it has been shown that the amplitude of a DPE is dependent on the amplitudes of the primary stimuli (Probst & Hauser, 1990). DPEs were evoked at levels in approximate proportion to the increase for low level primary tones. However for moderate primary tone levels, the level of growth either slowed or decreased for the DPE (Lonsbury-Martin et al., 1987; Furst et al., 1988; Smurzynski et al., 1990). As illustrated in Figure 1.9, the emissions at the lowest intensity levels are difficult to distinguish from the noise floor and then as they reach the higher intensities they are 20 - 30 dB above the noise floor. This figure also illustrates some of the different shapes or types of DPE growth curves as suggested by Nelson and Kimberley (1992) and Popelka et al. (1995).

The intensity of the primaries used to generate the DPE may be low (<60-70 dB SPL) or high (>60-70 dB SPL) and the resulting emissions would have categorically different features. The DPEs elicited from low stimulus levels have been reported to be dominated by active cochlear mechanical processes whereas the high stimulus level DPEs may be dominated by passive cochlear mechanics (Brown, 1987; Whitehead et al., 1990;

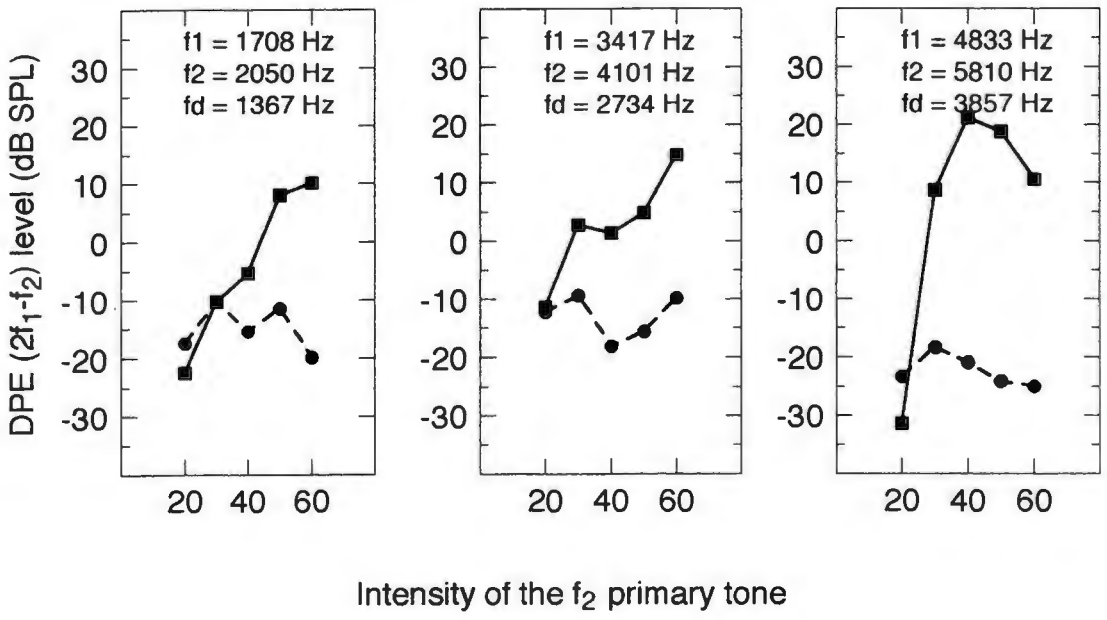


Figure 1.9 DPE growth function curves for 3 different f_2 frequencies from a 2 day old infant. The solid lines are the emissions (fd) and the dashed lines are the noise floor. Note the dip in the growth function curve at f_2 = 4101 Hz and the "roll-over" at f_2 = 5810.

1992a & b). These high intensity DPEs are less vulnerable than low-level DPEs and they have been shown not to be decreased by anoxia, noise overexposure, fatigue and trauma whereas the low-level DPEs in the same situation were reduced. However, the high level DPEs were decreased in amplitude by a combination of gentamicin and ethacrynic acid, two ototoxic agents that affect outer hair cells. DPEs have even been reported in dead ears when high intensity stimuli were used (Whitehead et al., 1992b; Brown, 1987; Schmiedt & Adams, 1980). Whitehead and colleagues (1992b) revealed that high intensity DPEs decrease much more slowly and with a more complex time course (i.e. within first 2 hrs.) post-mortem than do the low intensity DPEs.

The amplitude of the DPEs evoked by low stimulus levels ($\leq$ 62 dB SPL) was found to be strongly correlated with the auditory threshold at their geometric mean frequency. Avan and Bonfils (1993) suggested that the low stimulus level therefore would provide frequency-specific information on the local cochlear state. They also reported that DPEs elicited from high stimulus levels ($\geq$ 72 dB SPL) were not as sensitive to a decrease in hearing and this may be due to the broadening of the cochlear tuning.

In addition to the overall level of the primary tone stimuli, the level difference between the two primary tones can affect the amplitude of the emission. The intensity of the f_1 tone is denoted as L_1 and the intensity of the f_2 tone is L_2. For high stimulus levels, the maximum DPE amplitude was generated when $L_1=L_2$ (Rasmussen et al., 1993; Whitehead et al., 1995b). For low stimulus levels, the intensity of the primary tones was dependent on L_1 with the optimum level being $L_1>L_2$ by 15 dB (Gaskill & Brown, 1990; Whitehead et al., 1993; 1995a &b). The increase in DPE amplitude gained by decreasing the level of L_2 was small, i.e. > 3.5 dB at most frequencies (Whitehead et al., 1995a & b). However, Hauser and Probst (1991) reported that setting $L_1>L_2$ could improve the signal-to-noise ratios and therefore enhance the detectability of the DPE.

f_2/f_1 Ratio Effect

Maximum amplitude of the DPE is influenced by the ratio of the primary tones. In an early study, Wilson (1980b) reported that the maximum DPE amplitudes were found at f_2/f_1 ratios of 1.1 and 1.2. Since then optimum ratios have been studied by others and the general agreement was to use an f_2/f_1 ratio of ≈1.2 as shown in Table I.2. There is good agreement from these studies even though they were determined over different frequency ranges and with different methods. Harris et al. (1989) reported that the most effective f_2/f_1 ratio was 1.22. However, they described an inverse relationship between optimal f_2/f_1 ratio and the frequency of the DPE with larger ratios required at 1 kHz than at 4 kHz. The optimal f_2/f_1 ratio changed as a function of the intensity of the primary tones. As the intensity of the primary tones increased the f_2/f_1 ratio used to elicit maximal DPE amplitude also increased (Harris et al., 1989). Individual variability in the DPE amplitude has been noted regardless of the stimulus parameters used. This individuality in DPE response may be due to nulls, SOAEs or the microstructure of the individual's cochlea.

	Optimum Ratio
Kemp and Brown (1983)	1.250
Harris et al. (1989)	1.220
Gaskill & Brown (1990)	1.225
Bonfils et al. (1991)	1.220
Nielsen et al. (1993)	1.230

Table I.2 Optimum f_2/f_1 ratios which generate maximum DPE amplitudes.

The amplitude of the emission can be increased or decreased by factors relating to the individual. Nulls or monotonic dips can be observed in the DPE. These may occur in a "DP audiogram" at a single frequency as the DPE is measured across a series of frequencies. Gaskill and Brown (1990) reported that this was due to the f_2/f_1 ratio not having the ideal frequency separation to produce the optimum emission. They are also noticeable in DPE growth functions. In a growth function, as the emission increases with

an increase in the intensity of the primary tones some individuals may have a sudden decrease in the amplitude of the emission and then a return to the anticipated level (see Figure 1.9). These dips may be generated by phase cancellation between the acoustic components (Schmiedt, 1986b; Brown, 1987) or by the interaction of the two (i.e. low- and high-level stimuli) generators (Whitehead et al., 1990; 1992a & b) as discussed previously. In addition, a SOAE can enhance a DPE (Wit et al., 1981; Brown et al., 1994). If a SOAE occurred within ±50 Hz of the frequency of the DPE, the amplitude of the DPE would be enlarged (Wier et al., 1988). The emission would be influenced by the SOAE and cause the amplitude to be larger than normal.

Synchronized SOAEs can influence frequency content of TEOAEs, the spectral components of the SOAE are commonly found within the spectra of the TEOAE (Gobsch & Tietze, 1993). However, studies using aspirin have shown that SOAEs can be reduced but that the OAEs still may be present. Long and Tubis (1988) reported that aspirin reduced SOAEs and initially there was an increase in sensitivity in the threshold microstructure (i.e. a reduction in threshold) after which there was a reduction in sensitivity (threshold elevation). Eventually the EOAE disappeared into the noise floor and with it were decreases in the threshold microstructure, indicating that the mechanisms responsible for emissions were also involved with the threshold microstructure.

Noise floor

Another factor that can affect the amplitude of the emission and cause variability in the DPE is the noise floor. The noise floor is defined as the amplitude of background noise which occurs at or near the frequency in question at the time of recording. The emission is said to be present, if its amplitude is greater than that of the noise floor. However, at what point does one feel confident that the DPE is indeed a true emission and not random noise? The absolute noise floor is governed by the noise floor of the microphone. The DPE is

dependent on the noise floor and the sensitivity of the equipment used to measure it (Probst, 1990). Different algorithms have been developed to obtain estimates of the noise floor and variations in the average background noise levels are seen with different equipment.

To obtain the noise floor measurement, one method measures approximately 50, 100 and 150 Hz above and below the $2f_1$-f_2 frequency. These are averaged together for the duration of testing to yield the noise floor for that DPE frequency (CUBᵉDIS, 1992). Other methods of obtaining noise floor measurements have been reported. These vary from only measuring the amplitude of the signal 20 Hz below the DPE frequency (Lonsbury-Martin et al., 1990a) to estimating the noise floor by averaging eight frequencies below and eight frequencies above the DPE frequency (Whitehead et al., 1994b). The number of frequencies (or bins from the FFT) used to estimate the noise floor will affect the variability of the estimate. If the number of FFT bins is increased (to a maximum) then the variability in the noise floor decreases. The method used to determine the noise floor will influence whether an emission is present above the noise floor and therefore accepted as a true emission. If the noise floor estimate is too high then a true DPE may be masked by the background noise and thus create a false-negative response.

Once the noise floor has been estimated, the next consideration is to determine if the DPE is present or not. The amplitude difference between the noise floor and the emission will determine the false-positive rate. Differences of as little as 3 dB (Lonsbury-Martin et al., 1990a; Smurzynski, 1994) and as much as 11 dB (Popelka et al., 1995) have been suggested. The amplitude difference chosen as the cut-off for an emission to be present is important for the determination of the probability of a false-positive or a conversely a false-negative. As indicated above, the number of frequencies chosen to estimate the noise floor will influence the variance and therefore the amplitude difference required to determine if a DPE is present. The probability of reporting an emission when it is not actually present

(false-positive) is illustrated in Figure 1.10 for an algorithm that used six bins. The probability of reporting a false-positive decreases as the amplitude difference between the estimate of the noise floor and the DPE increases. If a DPE amplitude of 3 dB above the noise floor was used then the probability of saying a DPE is present when it is not would be approximately 18%. Increasing the difference between the DPE amplitude and the noise floor to 12 dB decreases the probability to approximately zero. If 3 dB were used then many false-positives would be reported and 12 dB would allow a large number of actual emissions to be missed when they are truly present. Based on the CUB^{e}DIS algorithm, an amplitude of 6 dB above the noise floor, would allow for a 5% probability of obtaining a emission when it is not present.

Most studies using adult subjects are performed in a sound-treated room, where the background noise is minimal and the subjects are cooperative. The results from testing in this type of location are reflected in the low noise floor measurements. Most newborn testing however, is done in the nursery or in a "quiet room", this increased the noise floor especially in the low frequencies. Popelka et al. (1995) reported that neonates can add as much as 15-30 dB of noise to the noise floor, making it more difficult to determine whether an emission is present above the noise floor.

ESTIMATES OF TRAVELING WAVE DELAY

Many different methods have been used to study the traveling wave delay, these include visual observation (Békésy, 1960), psychoacoustic estimation (Zerlin, 1969), single auditory nerve fiber discharges (Anderson et al., 1971), narrow-band Action Potential (AP) latencies (Eggermont, 1979 a & b), derived-band Auditory Brainstem Responses (ABR) (Don & Eggermont, 1978) and Evoked Otoacoustic Emissions (Wilson, 1980a; Kimberley et al., 1993). Traveling wave velocities have also been calculated based on derived whole nerve AP (Eggermont & Odenthal, 1974; Elberling, 1974), and derived

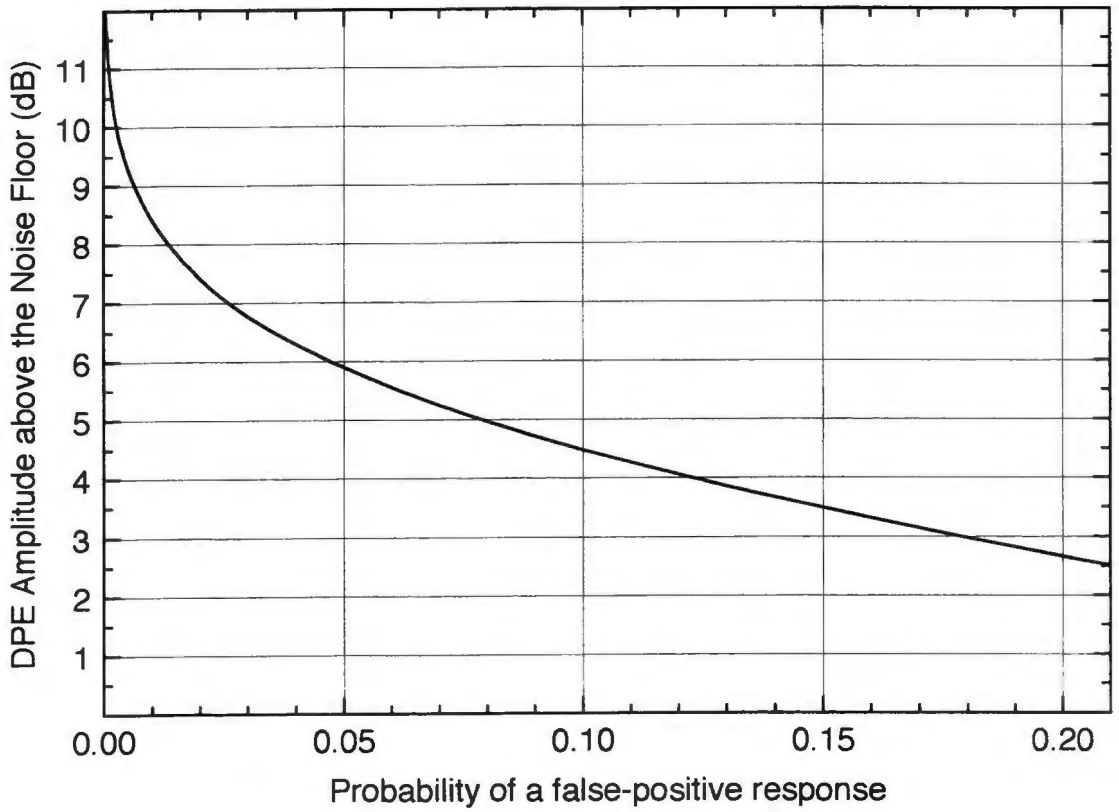


Figure 1.10 The probability of saying that a DPE is present when it is actually not is determined by the value chosen as the difference (in amplitude) between the DPE and the noise floor.

ABR (Parker & Thornton, 1978). These researchers found that the velocity of the traveling wave decreased from the basal portion to the apical portion of the cochlea. This data corresponded well with each other indicating activity at specific frequency regions as one moves apically along the cochlea.

TEOAEs have also been used to estimate the traveling wave delay in humans. Latency of different components of the TEOAE waveform is dependent on the frequency of the emission for TEOAEs (Wit & Ritsma, 1983; Probst et al., 1991). The re-emission from the cochlea is frequency specific and latency dependent. The TEOAE peak responses for high frequency components have a shorter latency than those with low frequency components (Wilson, 1980a; Wit & Ritsma, 1983; Neely et al., 1988; Zwicker, 1990; Probst et al., 1991). Johnsen and Elberling (1982b) also found that the response frequency tended to decrease when latency increased. However, they did not find the same clear-cut frequency/latency relation as did previous researchers. Latency values have varied across studies found in the literature, and are summarized in Table I.3. These estimates show greater travel times than those from evoked potential studies which may be due to the fact that they are highly variable as a function of method and stimulus level (Norton & Neely, 1987). These actual TEOAE latency measurements were not consistent with previous AP data. However, the stimulus intensity levels were different and if the emission data were compared with low intensity level AP data, then there was less discrepancy. TEOAE traveling wave delay from tone bursts was compared with ABR wave V latency (Neely et al., 1988). This study investigated the "forward" latency of the ABR, defined as the travel time from the onset of the stimulus to the characteristic place on the cochlea for a particular frequency component. They measured the wave V latency as the onset of the stimulus to the peak of wave V which really included the "forward" latency and some neural or synaptic latency. However the TEOAE measurement is from the onset of the stimulus to the first burst following the stimulus. This equates to an estimate of

round-trip latency for the TEOAE. Since the "forward" latency is a one-way estimate, they found that doubling the wave V "forward" latency would estimate the TEOAE latency.

Study	Latency at 1 kHz (ms)
Kemp (1978)	12
Wit & Ritsma (1980, 1983)	11
Rutten (1980)	10
Wilson (1980a)	10

Table 1.3 TEOAE latency in normal hearing human ears from different studies. Note that all used click stimuli.

The group latency technique uses the phase measurement to "count" the additional cycles of a tone as the frequency is increased (Kimberley et al., 1993). If the frequency of a tone is increased, then the number of cycles occurring within that time frame must increase. In order to determine the group latency, it is not necessary to know the absolute number of cycles that occur only the difference in phase between the different frequency tones. This difference in phase or cycles is plotted against the change in frequency creating a slope. The steepness of the slope indicates length of the delay, with steeper slopes having longer delays. In order for this technique to work, it is assumed that the phase-versus-frequency slope will be linear.

An estimate of the travel time of a mechanical disturbance between the oval window and any point on the cochlear partition can be determined by the slope of the phase-versus-frequency relationship. Phase-versus-frequency relationships are used to determine two types of delays:

(a) the phase delay $-\frac{\phi}{f} = \frac{\text{phase shift}}{360^\circ} \cdot \frac{1}{f\,(\text{kHz})}$ (1.6)

(b) the group delay $-\frac{d\phi}{df}$ (1.7)

where ϕ is the phase and f is the frequency. In cases where the phase-frequency relationship is linear then the phase delay and the group delay are the same.

For example, the amount of delay caused by a length of pipe can be estimated. To determine the delay using a click, one would need to measure the time it would take for the click to travel from the originating end until the sound emerges from the opposite end of the pipe. Another way would be to use continuous tones. To estimate the amount of delay of a sound traveling through a pipe using continuous tones, the phase of the sine wave could be used. Using a series of sine waves that are not harmonically related, the phase as a function of frequency is measured. Figure 1.11 illustrates how this can be accomplished. On the left hand side of Panel (a), there are five known frequencies being put into a tube, all of which start at the same phase. At the other end of the tube, the phase of each one is measured. The cumulative phase (in degrees) of each sine wave is plotted according to its frequency in Panel (b). A regression line fit to these points gives the slope of the line. Using formula 1.7, slope divided by degrees per Hz, the length of time it took to travel from one end of the tube to the other can be determined. From Figure 1.11(b), the slope is 35.8/360 degrees/Hz which equals 0.995 sec or 99.5 ms. In comparing this group latency (99.5) with the actual measurement 100 ms (Figure 1.11a), the group latency estimate is very close to the actual measurement. This phase-frequency technique can be used to measure the traveling wave delay from phase responses for various frequencies.

The DPE is representative of the cochlear place of the f_2 tone used to stimulate it (Brown & Gaskill, 1990). DPE phase measurements have also been used to estimate traveling wave delays. Kemp and Brown (1983) were the first to report the process of phase-versus-frequency relationships using DPEs. They showed the relationship for both holding the f_2 frequency constant while sweeping f_1 and for holding the f_1 constant and sweeping f_2. It was interesting to note that the direction of phase was negative when sweeping f_1 and positive while sweeping f_2. They reported that at the site of generation,

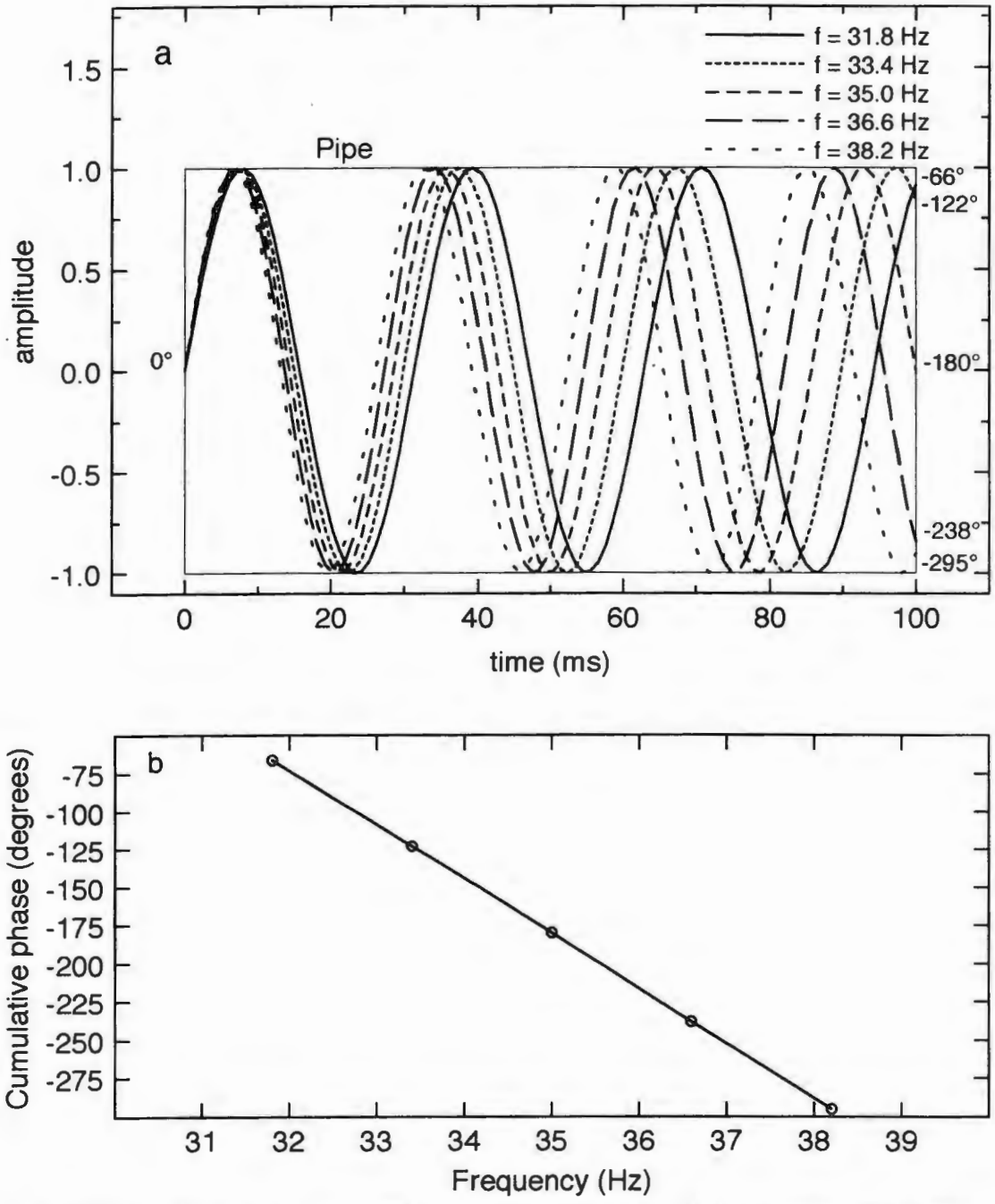


Figure 1.11 An example of estimating travel time through a pipe using DPE phase-versus-frequency measurements. (a) shows the measuring of the phase from the different tones. (b) shows the phase of the different tones and the regression line fit to this data.

the phase of the DPE was $2\emptyset f_1-\emptyset f_2+\emptyset dp$ when $\emptyset f_1$ and $\emptyset f_2$ were the stimulus phases at the interaction place. This indicated that there was a phase lag which includes the generation of the DPE as well as the reverse propagation of the DPE. However, they did not report any travel times with their data. Since this initial report others have estimated DPE round-trip travel times as illustrated in Figure 1.12. As shown, the estimated travel times from these different studies are very similar.

Kimberley et al. (1993) measured the phase-versus-frequency relationship for DPEs of various f_2 frequencies to determine the traveling wave delay for the human cochlea in normal hearing adults. The stimulus intensity was f_1 = 60 dB SPL and f_1 - f_2 = 15 dB SPL. The data were collected using a stimulus paradigm that held the f_2 frequency constant and swept the f_1 frequency. DPEs are a measure of pre-neural activity and do not include synaptic or neural delays but are measured in terms of a round-trip delay. They took half of the round-trip travel time and reported it as a one-way delay to be able to compare with other measurements. In doing this, their results were comparable with those of Eggermont (1979a). The effect of stimulus intensity on the round-trip travel time was studied and they reported that the delay decreased as the f_1 stimulus level was increased to 65 dB SPL.

Whitehead et al. (1994) looked at the phase-versus-frequency relationship of DPEs for both a "swept-f_1" and a "swept-f_2" paradigm in rabbit and human ears. The effect of stimulus intensity was studied in the rabbit, and it was noted that there was an increase in latency with a decrease in stimulus intensity from 75 to 45 dB SPL. They also measured direct onset latencies for the DPE and found good agreement between the directly measured onset latencies and the group latencies for the "swept-f_1" paradigm. They concluded that travel time increased with both decreasing frequency and decreasing intensity. In the "swept-f_1" paradigm they reported round-trip travel times between 8.39 and 2.39 ms for f_2 frequencies of 1.1 and 4.4 kHz respectively when using a stimulus intensity of 75 dB SPL. Travel times using the "swept-f_2" paradigm were longer at both frequencies. This is in

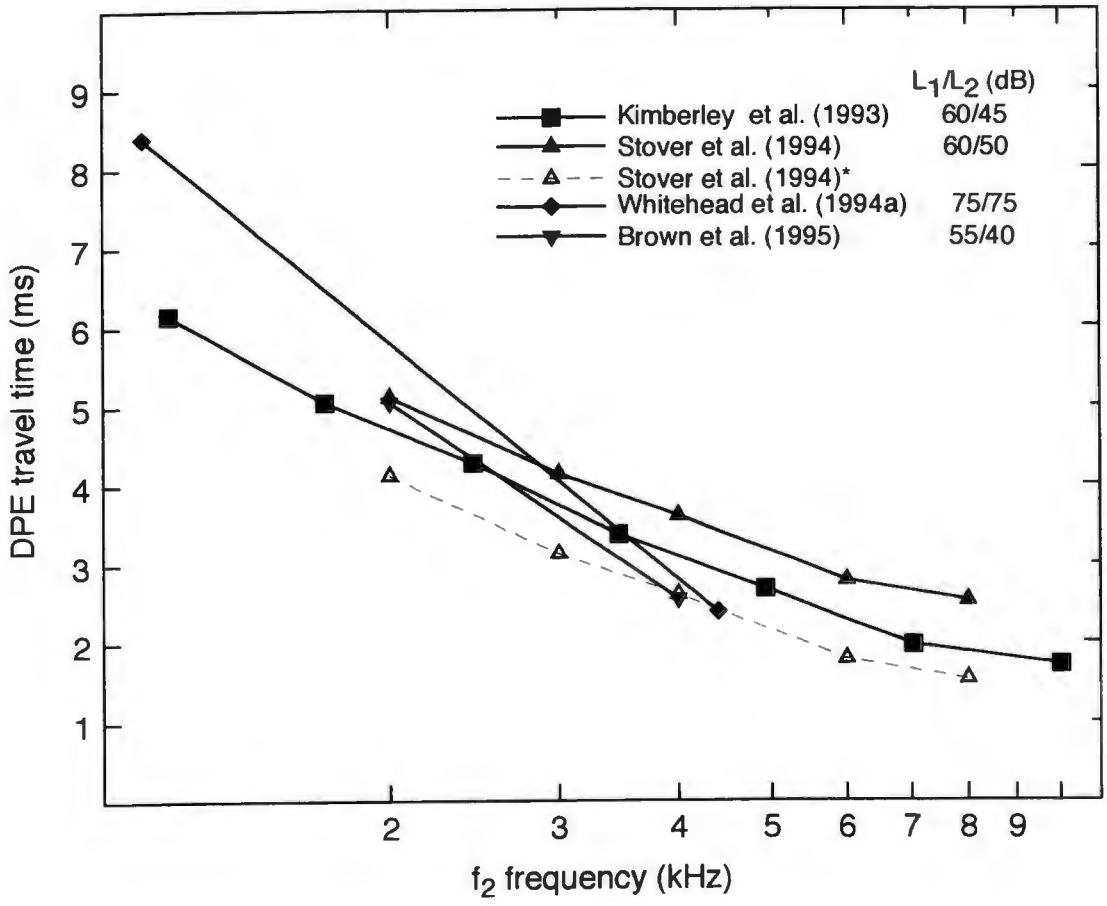


Figure 1.12 Estimated DPE round-trip travel times from normal hearing adults. *This data has 1 ms removed to account for acoustic propagation as suggested by the authors.

agreement with Mahoney and Kemp (1995), who suggested that the "swept-f_2" paradigm is more sensitive to the physiologically dependent aspects of cochlear mechanics (build-up time) and that the "swept-f_1" would underestimate the traveling wave delay.

Stover et al. (1994) studied round-trip DPE latencies by holding f_2 constant and sweeping f_1 from 2 to 8 kHz in half octave steps. They did this using stimulus intensities of L_1/L_2 beginning at 75/65 dB SPL and decreasing in 5 dB steps until no further responses could be recorded. The latency was determined as the primary peak of the inverse FFT of the group of DPEs associated with the fixed f_2 frequency. Although not stating actual levels, the results showed that there was an increase in latency as f_2 was decreased. They also found that the latency increased as the level of the stimulus decreased. They concluded that the latencies were "qualitatively and quantitatively" similar to those of Neely et al.(1988) and Kimberley et al. (1993).

DEVELOPMENTAL CHANGES IN THE HUMAN AUDITORY SYSTEM

The developmental process for the human auditory system begins in the third week and is considered to be functional by the last trimester (approximately 30 weeks conceptional age) (Rubel, 1978; Lavigne-Rebillard & Pujol, 1986; Lavigne-Rebillard & Pujol, 1987 ;Lavigne-Rebillard & Pujol, 1988; Zemlin, 1988). As previously noted, the ear is divided into sections; the external (or outer), the middle and inner ear, all of which develop along different time lines. However, the ear develops many of its structures concurrently as shown in the time line of the developing ear (see Figure 1.13). From the time of conception, it is about three weeks until the first stages of ear development commence. The first structure to begin development is the inner ear and it is also the last to complete development.

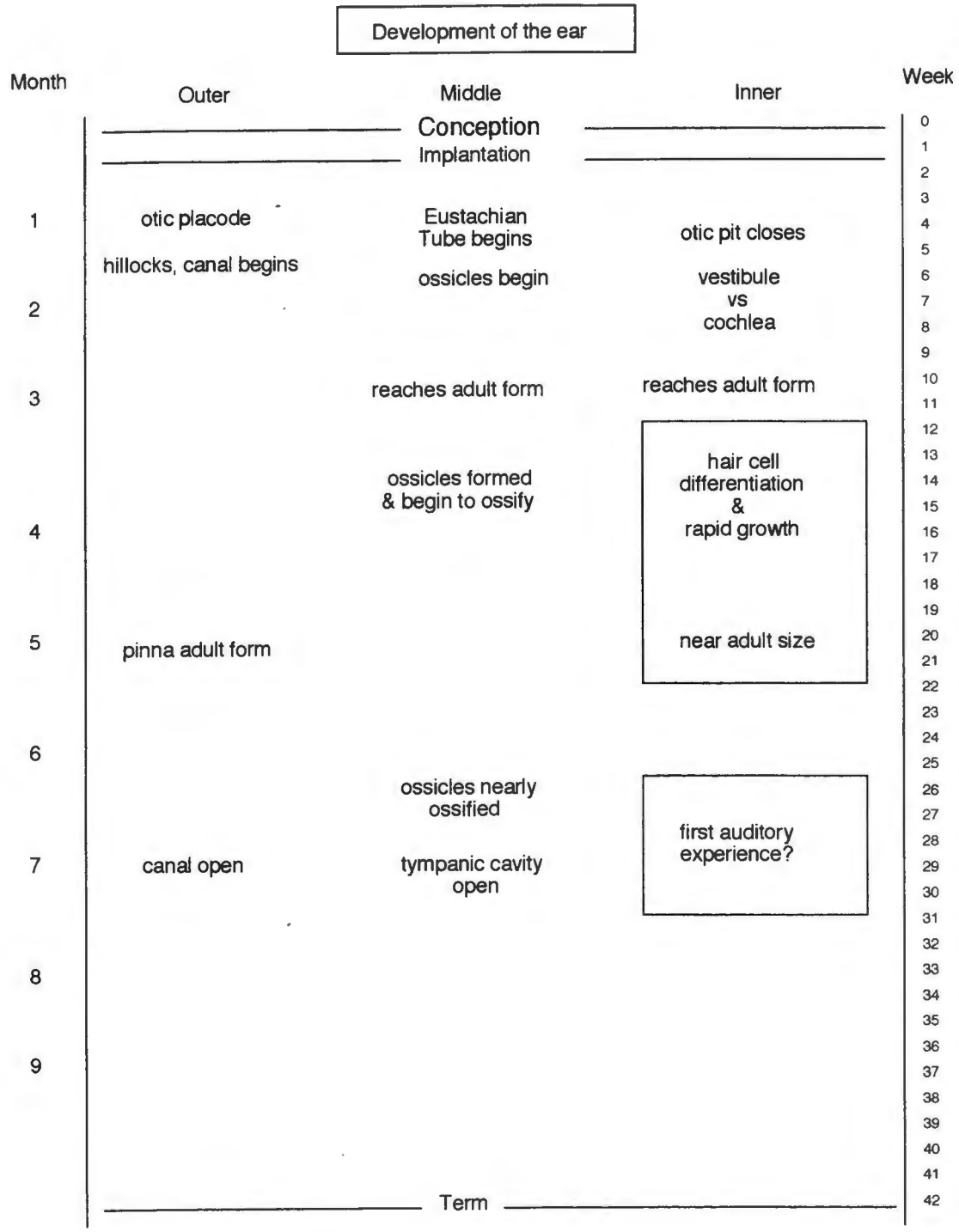


Figure 1.13 Time line for development of the human ear from conception to term birth.

External Ear

The outer ear begins development in the fifth week after conception. It can be seen that there is thickening of tissue in the form of six hillocks in the area of the first and second branchial arches. These hillocks or "little hills" will become the pinna and tragus. The pinna has essentially adult form and location by week 20 but will continue to grow until approximately 9 years of age (Kenna, 1990).

The external auditory meatus develops from the widening and inward extension of the first branchial groove. The ectoderm from the first branchial groove makes contact with the endoderm (internal embryonic germ layer) of the first pharyngeal pouch and forms a membrane. However, mesoderm moves in between these two layers and separates them for several months. In the eighth week, the groove deepens forming the primary meatus. It deepens further in the next week allowing for a solid epidermal plug to form from the primary meatus to the middle ear. At week 21 these cells begin to re-absorb allowing space for the formation of the external auditory canal (Kenna, 1990).

Middle Ear

During the fourth week, the middle ear develops from the inside in an outward direction, which is to say that the endodermal pharyngeal pouch evaginates. This first pharyngeal pouch extends laterally to form the tubotympanic recess in what will become the eustachian tube and the tympanic cavity.

The tympanic membrane is still surrounded by mesoderm but between the 11th and 16th weeks triples in diameter. By week 19, its shape is completed, however its orientation is nearly horizontal. It has been suggested by Eby and Nadol (1986) that this change in tympanic membrane orientation may alter the orientation of the ossicles. Tissue is absorbed from the tympanic space medially and from the branchial groove laterally up to week 28 to 30, when the external auditory meatus is open and only the tympanic membrane remains. The tympanic membrane slowly moves more vertically until age three when it has

obtained its adult shape (curvature) and position (Balkany et al., 1978; Anson et al., 1991; Peck, 1994b).

In the fifth and sixth weeks, the ossicles begin development from a concentration of mesenchymal cells which lie between the embryonic inner ear and the first branchial groove (Peck, 1994b). The head and neck of the malleus and body of the incus have been shown to arise from the first branchial arch. The handle of the malleus, long process of incus and crura of the stapes arise from the second branchial arch and the footplate of the stapes comes from the second arch and the medial surface of the otic capsule (Kenna, 1990). The development of the ossicles occurs in mesenchymal tissue, which is reabsorbed between weeks 12 and 28, opening the tympanic space which allows room for movement of the ossicles. Some tissue and fluid may remain even after birth however, it is quickly replaced by air. The ossicles appear nearly adult size and shape by the 15th week. Ossification of the ossicles begins in week 15, bone appears in the malleus and incus in week 16 and they are ossified by week 26. However, bone does not appear in the stapes until week 19 and ossification continues up into adulthood (Anson et al., 1991).

Inner ear

The first event in the development of the auditory system is when the ectoderm or outside layer of germ tissue begins thickening on each side of the cephalic (head) end of the embryo (Peck, 1994b). The otic placode invaginates and by the fourth week closes in upon itself to form the otic pit. When the otic pit is completely closed in and cut off from the surface, it forms the otic vesicle (Anson et al., 1991). This vesicle then migrates inward to form the inner ear. During the fourth week, the ganglion cells from the VIII th nerve arise from the otic vesicle.

Soon after the closing off of the otic vesicle, it begins elongating and both vestibular and cochlear portions of the labyrinth are distinguishable (Kenna, 1990). By week 7, the semicircular canals and the first cochlear turn has developed. In addition, it

has been shown that nerve fibers begin to enter the expanding cochlea at this time (Rubel, 1978). The labyrinth grows quickly and the cochlea changes from having only one turn to its adult-like shape of two and a half turns by the end of the first trimester.

In the cochlea there is a differentiation of cells caused from a thickening of the epithelium of the cochlear duct. The shape of the duct changes to triangular with the fusing of the three walls which become Reissner's membrane, BM and the spiral ligament (Anson et al., 1991). In week 9 the tectorial membrane can be observed, it is the first structure of the organ of Corti that can be recognized. It develops in a base to apex gradient and by week 13 -15, has extended throughout the cochlea (Lavigne-Rebillard & Pujol, 1987). The differentiation within the organ of Corti continues from week 9 to 22 so that there are distinct receptor and supporting cells. This differentiation has been shown to develop in the different cochlear turns at different times. The apical turn is the first to show a thickening of the epithelium, an ill-defined gelatinous tectorial membrane and a bulging and loosening of cells in the OHC area. As a part of this differentiation of cells and with the same gradient, ciliogenesis occurs on the surface of the IHC during week 11 and on the OHC during week 12. Both types, IHC and OHC, had an adult stereocilia pattern by 20 to 22 weeks. However, Lavigne-Rebillard & Pujol, (1986) reported that there were still signs of immaturity suggesting that maturation may not be complete until the last trimester. The afferent fibers can be seen at the base of both IHC and OHC by before the development of the stereocilia. The efferent fibers were only located below the IHC by week 14 but by week 22 the synapses between the efferents and the OHC were present (Lavigne-Rebillard & Pujol, 1988). At week 16, the Tunnel of Corti begins to appear in the basal turn but not at the apical end. During the next 4 weeks the organ progressively completes its development toward the apical end and by week 21 the tunnel of Corti is present in all turns. Myelination of the osseous spiral lamina had begun but was not complete by week 22 (Lavigne-Rebillard & Pujol, 1988). As the labyrinth nears adult size, it is completely

encased in its bony capsule and is basically equipped and ready for sending afferent signals at approximately 24 weeks (Igarashi & Ishii, 1980).

MATURATION OF THE AUDITORY SYSTEM

The cochlea is the last part to become functional during ontogenesis of the auditory system (Romand, 1983). The nerve fibers are present in all the turns of the cochlea at 12 weeks conceptional age and by 24 weeks the appearance of the organ of Corti can be described as adult-like. Within the developing cochlea, many processes occur first in the basal or mid-basal turn and last at the apex. These include: differentiation and innervation of the hair cells, development of the spaces of Nuel, opening of the tunnel of Corti, formation of the inner spiral sulcus, and differentiation of the stria vascularis (Rubel, 1978).

Other structures within the organ of Corti to develop during this period are the hair cells. The inner hair cells (IHC) can be recognized prior to outer hair cells (OHC) and there is a basal-to-apical differentiation of IHC prior to that of the OHC. In addition, the IHC receive innervation from the afferent fibers slightly before the OHC (Rubel, 1978, Lavigne-Rebillard & Pujol, 1988). In the early development of the hair cells, both afferent and efferent nerve fibers are connected to the inner and outer hair cells.

In conjunction with the IHC, the number of afferent fibers increases and the number of efferent fibers decreases. The efferent fibers for the IHC are not connected to the cell but are restricted to the afferent dendrites (Romand, 1983). As with the connection at the IHC, the efferents and afferents for the OHC compete with each other for occupation on the hair cell membrane. However, the efferent fibers are delayed in connecting to the OHC. In contrast to the IHC, the efferent fibers form two or three large connections directly with the OHC whereas the afferent fibers, although directly connected to the OHC, decrease in number.

The cochlea is organized tonotopically, which is apparent as early as neuronal responses to stimulation can be elicited from the central nervous system. This spatial development of the cochlea has been shown to proceed in two directions, one is basal and the other is apical. In the immature cochlea, the basilar portion is first to transduce mechanical vibrations into neural signals. In the adult cochlea this portion would respond to high frequencies, however, the immaturity of the structure causes the response to be primarily restricted to low frequency sounds (Rubel, 1978). The region which is responsive to a given frequency may shift during development.

Rubel (1978) proposed that there is a shift in the frequency response of the cochlea. During maturation of the cochlea, the basal portion is initially tuned to lower frequencies than it is at the end of the maturational stage. The developing cochlea is most responsive to sound in the mature region or near the middle of the basal turn and then towards the basal one-third of the cochlea. Therefore, the extreme high frequencies would be the last to reliably elicit an auditory response. Rubel and his colleagues (Rubel & Ryals, 1983; Lippe & Rubel, 1983; Rubel et al., 1984) have shown that a systematic apical shift occurs in the position of hair cell loss, and tonotopic organization as a function of age. This suggests that the spatial encoding of frequency along the basilar membrane is not fixed but changes during development of the auditory system. Further studies by Norton et al. (1991) using DPEs, have shown that in the developing gerbil emissions appear first in the high frequencies (basal turn) and last in low frequencies (apical turn).

In the early stage of cochlear development, the high frequency or basal region of the cochlea would be expected to develop first. However, only responses for low or medium frequencies can be obtained which suggests there is a developmental process for tuning in the auditory system. Romand (1983) has shown that tuning is very broad in the immature cochlea of the kitten. He compared threshold development related to the characteristic frequency (CF) for tuning curves. When measuring tuning curves for the high frequency

region, the only responses he obtained were in the tail or low frequency region. As development continues, the frequency selectivity sharpens and the tip of the tuning curve appears. During the next three weeks, the basal region responds to medium and high-CF units (2-10 kHz).

Romand (1987) proposed that at the onset of cochlear function, the OHC are still immature and that only the IHC are ready to function. Tuning of the cochlea must then rely on only the passive mechanism until the OHC mature. The active mechanism which occurs with the maturation of the OHC sharpens the tuning of the cochlea forming the tip of the tuning curve. This will cause the site of activation to shift to a more apical location for a particular frequency.

Methodologies for Evaluating Maturation of the Auditory System

Recently additional information on development of the auditory system has come from studies which compare infants and adults using different test procedures. These tests which measure different aspects of the system are Spontaneous Otoacoustic Emissions, Evoked Otoacoustic Emissions, Reflectance measurements and Auditory Brainstem Response testing.

Spontaneous Otoacoustic Emissions

SOAEs measured in infants one month of age have been compared to SOAEs from adults (Burns et al., 1992a). The prevalence of SOAEs in one month olds was the same as in the adult population. However, Burns et al. (1992a) found that the predominant SOAE frequency range was higher and the amplitude of the SOAE were greater in the infant group. The majority of the SOAEs from the adult group were between 1.0 and 2.0 kHz whereas in the infant group they were between 2.5 and 5.0 kHz. Likewise the average

amplitude of the SOAE was -2.6 dB SPL for the adult group as compared with 8.5 dB SPL for the one month olds. They stated that the SOAEs are a byproduct of normal cochlear function since the prevalence was the same as that of normal hearing adults. In a follow-up study, Burns et al. (1994) compared SOAEs from six, 12 and 24 month olds. They found that the SOAEs were stable in frequency but that there was some decrease in amplitude as age increased. However, the frequency and amplitude levels from the 24 month olds was still not adult-like. This lack of shift in frequency and only a gradual decrease in amplitude suggests that there is no development at the cochlear level over this time period but that the level difference must be from developmental changes in the external and/or middle ear.

Evoked Otoacoustic Emissions

It has been shown by many researchers (Kemp, 1989; Chuang et al., 1993; Collet et al., 1993; Norton & Widen, 1990) that evoked emissions can be recorded from neonates and that these emissions are larger in amplitude than those from adult ears. This is often explained on the basis of a difference in the size of the external ear. It has also been reported that the click EOAE response becomes larger in amplitude and that more infants pass an EOAE screening on the second or third day postpartum (Kok et al., 1992; Thornton et al., 1993). This change in EOAEs was suggested to be maturational and not due to any changes in external or middle ear properties such as middle ear pressure or vernix in the ear canal even though they found that these factors could account for some of the change (Johnsen et al., 1989; Chuang et al., 1993; Thornton et al., 1993). However, temporary hypoxia may also account for this change in emission amplitude.

Maturation of the human cochlea was studied by measuring the traveling wave delay using derived-band ABR (Eggermont et al., 1991). This delay was estimated by finding the wave I latencies from one derived band and taking the difference between

adjacent derived bands. They found that the delay between the octave bands with CF of 11.3 kHz and those with CF of 5.7 kHz reached adult values at 3-6 months of age.

Brown et al. (1995) investigated differences in the mechanical response of the cochlea between infants and adults. Their results suggested that the mean group delay at both 2 and 4 kHz (f_2 frequency) was significantly greater in infants than in adults. The infants were grouped into two groups, a preterm (31-37 wks.) and term (38-42 wks.) group. However, due to the small number of responses at each frequency, these two groups were averaged together to form an infant group for the comparison with the adult group. They also reported that the difference between the mean group delays at 2 and 4 kHz was significantly greater for the infants as compared with the adult group. These differences suggested that the difference was at the cochlear level.

Reflectance Measurements

Keefe et al. (1993) studied the development of the external ear canal and middle ear in infants up to 24 months of age and in adults using impedance and reflection coefficient responses. They found that this development was not yet complete by 24 months. The input impedance and the reflection coefficient responses were affected by growth of the ear canal and middle ear cavity which has been shown to change over this time period. Eby and Nadol (1986) for example, used radiographic measurements and found that the distance from the stapes footplate to the tympanic membrane grew in the first six months postnatally. Keefe et al. (1993) also found that the power transfer into the middle ear of infants was less than that of adults. They suggested that this difference in power transfer may also account for the difference seen in thresholds between infants and adults.

Auditory Brainstem Response

Maturation of the auditory system has also been studied using the Auditory Brainstem Response (ABR). Results generally suggest that there is a decrease in latency of the ABR components with increasing age (Gorga et al., 1987; Eggermont, 1989).

Eggermont and Salamy (1988a & b) investigated the changes in click ABR between preterm and term born neonates. They revealed that the absolute values for waves I and V were significantly longer in the preterm groups than in the full term group. However, the I-V interpeak latency did not differ between the groups. This lead them to conclude that prematurity was not the cause of the different maturity rates noted in the absolute latencies of the ABR but that the differences could be explained on the basis that preterm infants at 40 weeks CA had a higher incidence of otitis media or middle ear effusions.

The click ABR wave I has been shown not to change in infants of full term which supports the concept that the cochlea is very close to maturity when the infant reaches term (Eggermont, 1992). However, Eggermont et al. (1991) observed that there was a change for certain frequency ranges. They noted using derived band ABR that the high frequencies, corresponding to the basal portion of the cochlea reached adult values first and that by 3-6 months of age the frequencies found in the apical end would reach adult values. Changes in wave I reflect what is happening with the auditory brainstem structures. The changes for wave V, reflecting maturation in the lower brainstem, do not mature at the same time as wave I but take approximately 3-5 years until they reach adult values.

RATIONALE FOR THE PRESENT STUDY

de Boer (1979) suggested that it was important to measure cochlear frequency selectivity directly. Although research using cochlear action potentials and AP tuning curves has been found to be useful for assessing the state of the cochlea, he felt they were not accurate enough and that new and different procedures needed to be developed. Since

that time, Kemp and Brown (1983) proposed that the DPE phenomenon could be used as a probe with which to explore cochlear wave propagation times. This new method utilizing DPEs to measure the round-trip travel time would add additional information about the maturation of the cochlea.

Although the cochlea is considered functional at birth, ABR studies (Eggermont et al., 1991) have reported developmental changes up to 3 to 6 months. Brown et al. (1994) using DPE estimated mean group delays revealed that the mechanical response of the cochlea for term-born infants was still immature at least in the 4 kHz region. They suggested that this was a cochlear maturation and not a purely conductive problem.

This present study will extend the understanding of the maturation of the cochlear mechanisms. Cochlear travel times will be measured across a large frequency span in infants and adults. No other study has reported measuring DPE estimated travel times in pre-mature infants as young as 30 - 33 weeks conceptional age (CA). CA is defined as the age in weeks between conception and the time of testing (Eggermont, 1989)

Few reports are available that studied DPEs in term or preterm infants (Lafreniere et al., 1991; Lasky et al., 1992; Smurzynski, 1994). The parameters used to test these neonates were the same as in adults. Lafreniere et al. (1991) tested newborns with a f_2/f_1 ratio of 1.2 because that was optimal for the majority of adults but suggested that this characteristic has not been fully studied in the newborn population. Other reports (Lafreniere et al., 1991; Brown et al., 1994) have shown that emission amplitudes were larger in infants than in adults. Based on Lafreniere et al. (1991) it is expected that the emissions from term-born infants will be larger in amplitude than those of the adults below 4 kHz but not above 4 kHz.

OUTLINE OF PRESENT INVESTIGATION

The beginning phase of this study was to determine if group delays or latencies could be calculated from DPE measurements. Initially, DPEs using the "sweep-f_1" technique were recorded from a group of normal hearing adults and round-trip travel times were calculated from this data. The results from this DPE technique were compared to Eggermont's (1979a) electrocochleagraphic data (Kimberley et al., 1993). Although there was good agreement between the two studies, there were differences between the techniques. DPEs are a direct measure of pre-synaptic cochlear function but include a round-trip travel time not just a one-way trip. This makes it difficult to compare to other methods, especially those utilizing evoked potentials which include synaptic delays. In addition, most studies using evoked potentials were done with high level stimuli whereas DPEs use low-level stimuli, and this could affect the delay values.

DPEs will be measured from a population of infants ranging in age from 30 to 42 weeks CA and from a group of normal hearing adults. Two different measures of DPEs will be taken, one using the "DP audiogram" and the other with the "sweep-f_1" technique. Low-level stimuli will be used to ensure that the "active mechanism" will be evoked and that only one generating source will be measured.

The first hypothesis tested in the present study is the dependence of DPE phase on DPE frequency for different age groups. If the cochlea is developed before 42 weeks CA, then there will be no difference in the latency of the travel time between the term born baby and the adult. Travel times between the preterm groups may give information in regards to the "shifting place principle" and the changes that are proposed to occur in the high frequencies. The second hypothesis tested is the dependence of DPE phase on DPE frequency at various intensities of the stimulus for the adult group. If intensity of the stimuli has no effect on the travel time then the model of round trip travel times will not be made up of travel time and a filter delay. Furthermore, if a difference between the travel

times of infants and adults is found then the effect of intensity may help in ruling out changes due to conductive losses in the infants. This is so as long as it is can be assumed that decreasing the amplitude of the stimuli is equivalent to a conductive hearing loss. These round-trip travel times for the different age groups will be compared with other measures using different techniques.

Thirdly, what is the optimum ratio of f_2/f_1 which generates the largest emission amplitude for each group? If the optimum ratio does not change with age then different stimulus parameters will not be required for clinical testing with DPEs for different age groups. Also, a change in the optimum ratio, if influenced by the developmental process, would indicate that there is change in BM tuning or in the overlap required to generate maximal DPE amplitude. Finally, if normal hearing is considered to be threshold of the young adult then maximum amplitude of the emission should be seen with this group. The amplitude of the emissions corresponding to the DPE frequency for a given f_2 should either not differ or increase with age.

Chapter 2. METHODS

EQUIPMENT

Hardware

Distortion Product Emissions were measured from all subjects using a system which was comprised of an IBM-compatible computer with an Ariel DSP-16+ (Version G) signal processing board, a probe assembly comprised of two insert ear phones (ETYMOTIC RESEARCH ER-2) and a low noise microphone with a preamplifier (ETYMOTIC RESEARCH ER-10B). The Digital Signal Processing (DSP) board which plugs into the computer has a TMS-320C25 DSP chip, 2 MBytes of memory, dual 16 bit "CD-Quality" analog to digital (A/D) and dual 16 bit digital to analog (A/D) converters (CUB^{e}DIS™, 1992). A block diagram of this equipment is shown in Figure 2.1. The equipment used in this study is commercially available, however, the software was customized to obtain the extra phase measurements.

Software

The two computer programs used to collect the DPE data are from the CUB^{e}DIS© software developed by AT&T Bell Labs (CUB^{e}DIS™, 1992). The 'CUBDISP' program was used as a screening for each subject to determine if they had emissions present. The program consists of two stimulus tones with a f_2/f_1 ratio of 1.2 that are swept from 10 to 1 kHz with seven frequencies per octave. The twelve pairs of primary tones were presented at two different levels for all f_2 frequencies; (1) f_2 = 55 dB SPL where f_1-f_2= 10 dB; and, (2) f_2 = 50 dB SPL where f_1-f_2= 15 dB. The DPE, $2f_1$-f_2, is plotted according to its f_2 frequency. The noise floor is also plotted and an emission must be 5 dB greater than the background noise to be considered present.

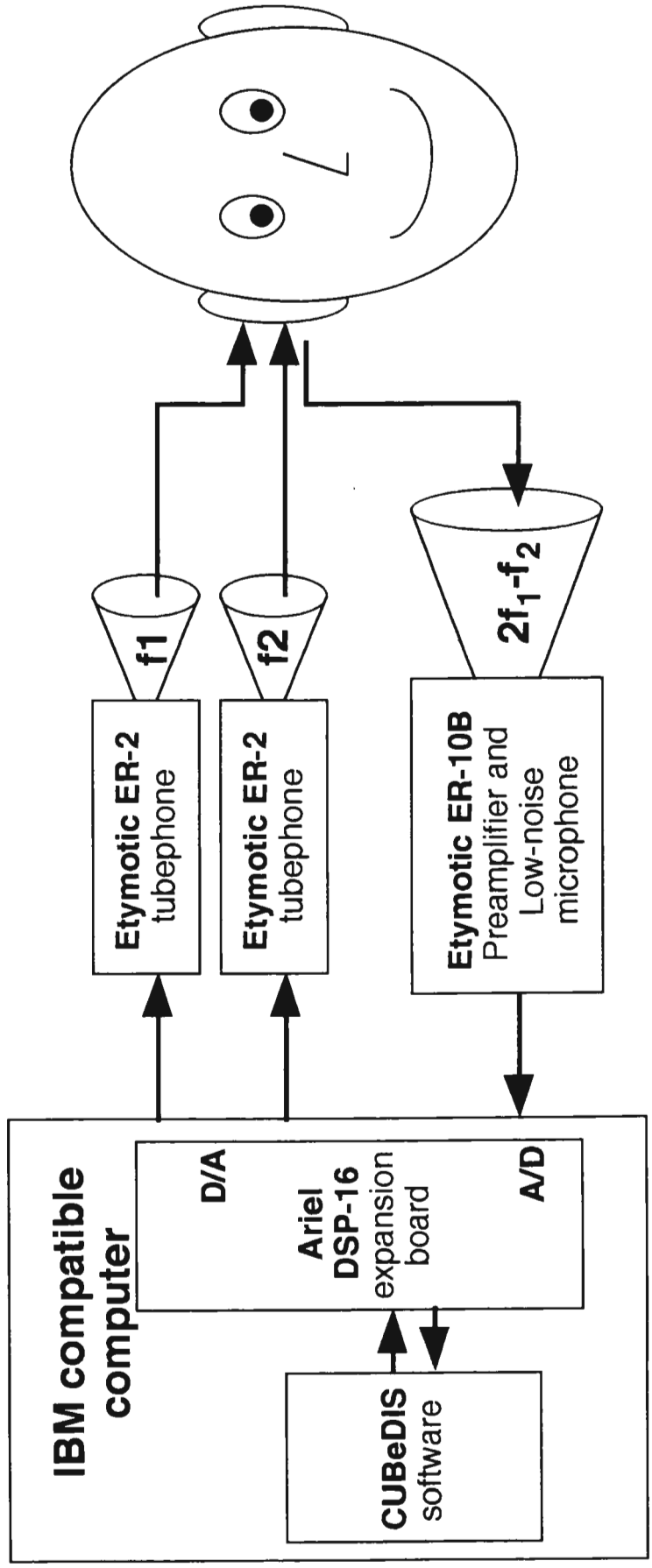


Figure 2.1 Block diagram of DPE test equipment.

The 'CUBDISD' computer program which was used, is a modification of the 'CUBDISF1' from the CUB^{e}DIS© software developed by AT&T Bell Labs (CUB^{e}DIS™, 1992). This program allows the user to change many of the parameters in order to record a DPE. The tones consist of a probe or f_2 tone which is held at a constant frequency and the variable or f_1 tone which is varied around it at an f_2/f_1 ratio of 1.3 to 1.1. The tones were presented 15 dB apart with the f_2 level at 45 dB SPL. There were six different f_2 probe tones equidistantly spaced on a logarithmic scale between 1.7 and 10 kHz. Frequencies below this level were not used because they could not be reliably recorded in the preterm and term groups due to the level of background noise in the nurseries.

SIGNAL GENERATION AND STIMULUS PARAMETERS

In order to obtain a DPE two tones must be sent to the ear of the subject and the response recorded. As shown in Figure 2.2, this process was accomplished by having the computer generate two tones, send them to the DSP board and play the signals (output) on the two 16-bit D/A converters in a periodic manner. The signals were controlled so that the sound pressure in the ear canal was kept constant across the frequency range required. The signals from the ear canal were recorded using the ER-10B low noise microphone and sent to the pre-amplifier. The gain of the amplifier was set to 40 dB SPL and the output was sent to the A/D converters on the DSP board. The responses (input) were averaged on the DSP chip in real time in a synchronous manner.

The output was in the form of two sine waves at different frequencies, f_1 and f_2, where f_1 is lower in frequency than f_2 and f_2 is lower in intensity than f_1. These two simultaneously presented tones were mixed acoustically in the ear canal. The maximum output of the ER-2 tubephones (receivers) is approximately 70 dB SPL due to a slight modification in the sound delivery tube which tapers it down to about 1 mm. This modification of the tube raises the source impedance considerably which reduces the chance

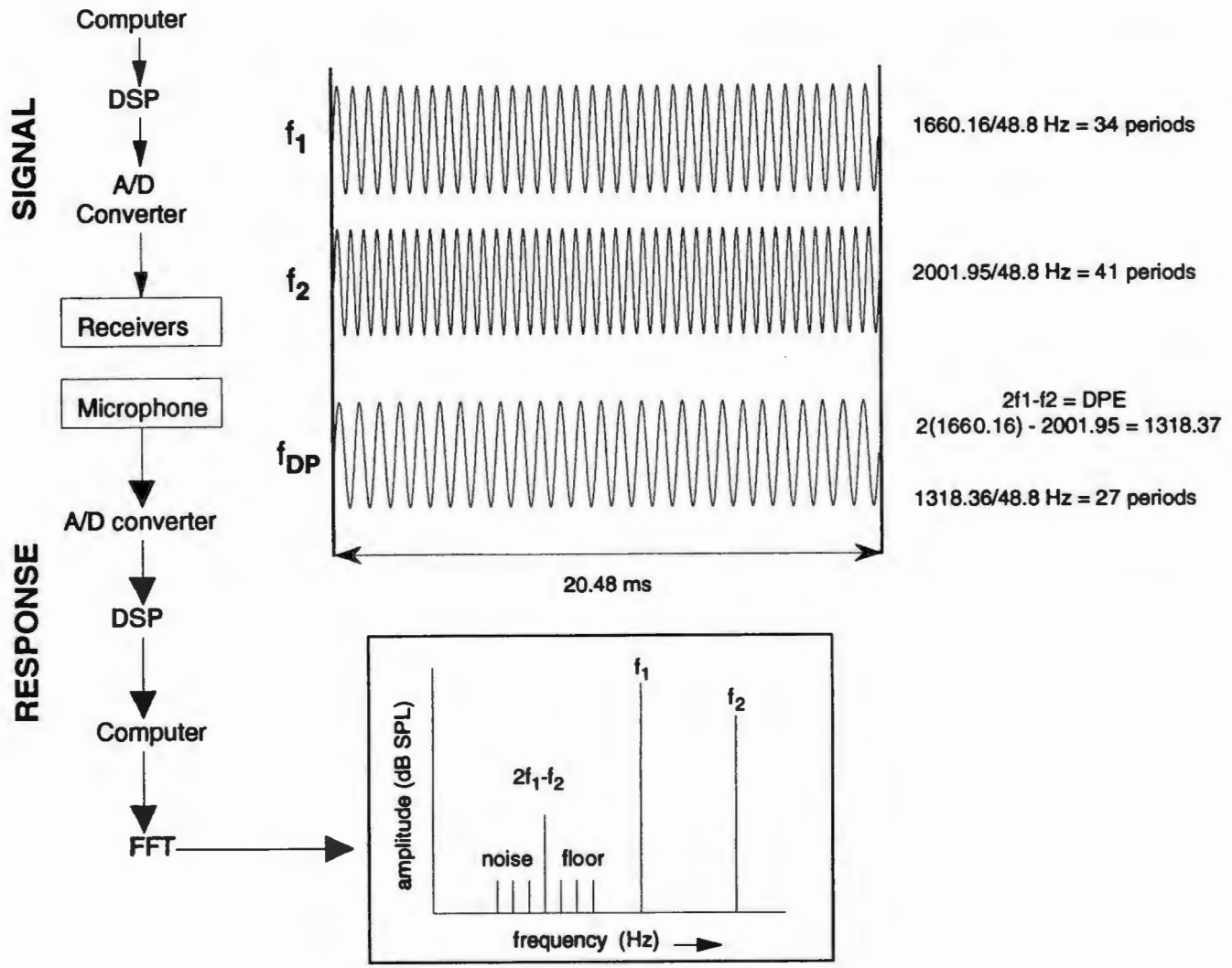


Figure 2.2 Block diagram showing generation of signal and collection of response from the CUB^{e}DIS system.

of intermodulation distortion caused by any acoustic cross talk coming from the receivers.

The output signals are placed in 1024 point buffers or arrays in the memory of the DSP board. The sampling rate of the board is 50 kHz which allows for an array of 20.48 ms. The array has a bandwidth of 48.8 Hz (sample rate 50000 Hz/1024 point array = 48.8 Hz). This means that when the user specifies a frequency, the program rounds it off to the closest multiple of 48.8 Hz. This allows the sample to fit exactly within the array, and if both tones (f_1 and f_2) are multiples of 48.8 Hz then the $2f_1$-f_2 emission will also be a multiple of 48.8 Hz. The buffer is repetitively played out, one on each channel (receiver) to produce the signal. The response from the microphone is periodically time averaged for 200 averages or 4.096 seconds of data ([20.48 ms * 200 averages]/1000 ms/sec = 4.096 sec). The $2f_1$-f_2 emission is a multiple of 48.8 Hz and therefore will also fit exactly into the window requiring no windowing, thus producing a lower overall noise floor. The array is sent back to the computer where the Fast Fourier Transform (FFT) is performed with a spectrum sampled every 20.48 ms.

The amplitudes of the DPE and the background noise are measured simultaneously, ensuring that any extraneous or subject noise will affect both in the same manner. The noise floor was calculated by measuring the amplitude at six frequencies around the $2f_1$-f_2 frequency and averaging the six FFT bins together. Measurements are made approximately 50, 100 and 150 Hz above and below the $2f_1$-f_2 frequency, then averaged together to calculate the noise floor. This assumes that they are independent estimates of the noise thereby reducing the variance of the noise floor by the $\sqrt{6}$. The system also uses a noise rejection algorithm which was set at zero dB SPL. The noise rejection works by taking the number of averages (200) and dividing them into four smaller blocks of fifty averages each. The computer averages one block and then compares this average noise floor amplitude to the zero dB SPL maximum allowable noise level. If the amplitude of the noise is less than that of the level set by the user, it is accepted. If the amplitude of the noise is

greater than that of the maximum allowable noise level, then it is rejected and a new block is recorded. This process continues until four blocks have been accepted or a maximum number of rejects (CUBDISD = 16 and CUBDISP = 10) has been reached . Once the number of maximum rejects has been reached, the system averages only the blocks that have been accepted and moves onto the next frequency to be tested.

To determine the dependence of DPE phase on DPE frequency at various intensities of the stimulus, one ear from a group of forty normal hearing (>20 dB hearing level) adults (see Table II.3) were tested using the modified 'CUBDISD' program. This program uses the "sweep-f_1" technique, which held the intensity of the primary tones constant but swept the f_1 frequency around the f_2 frequency from a ratio of 1.3 to 1.1 for six different f_2 frequencies. The stimuli were presented 15 dB apart but the intensity of the primary tones, f_2 and f_1, were varied. The stimuli ranged between 20 and 45 dB SPL for the f_2 frequency in 5 dB steps.

The dependence of DPE phase on DPE frequency was recorded from four different age groups from preterm to adult. There were 348 ears tested but only 145 ears were used across the four groups (see Table II.2). The subject was tested at each of the six f_2 frequencies, 10.0089, 7.0313, 4.9316, 3.4668, 2.4414 and 1.709 kHz. Again, the f_1 frequency was swept around the f_2 frequency from a ratio of 1.3 to 1.1 for the six different f_2 frequencies, the f_1 stimuli was 15 dB greater than the f_2 which was 45 dB SPL across all frequencies tested.

The optimum f_2/f_1 ratio was also compared across frequency and age group, This ratio is the ratio between the two primary tones (f_2 and f_1) which creates the largest amplitude $2f_1$-f_2 (DPE) emission. The f_2 frequency is fixed at a given frequency, and the f_1 frequency is changed from a ratio of 1.3 to 1.1, the largest amplitude emission can be seen for some intermediate value. The intensity of the primaries were kept constant at 45 dB SPL for the f_2 and the f_1-f_2 = 15 dB.

The amplitude of the emissions were measured at two different intensity levels while sweeping across the frequencies for the four different age groups. The stimuli were swept from 10.0098 kHz to 1.709 kHz with 2 points per octave and the f_2/f_1 ratio was 1.2. The stimulus level of the primaries was f_1 = 65 dB SPL with f_1-f_2 = 10 and f_1-f_2 = 15 dB. The resulting emission had 12 DPE frequencies and noise floor values which were plotted for their corresponding f_2 frequency.

DATA COLLECTION PROCEDURES

Calibration

The probe assembly was inserted in a subject's ear canal to calibrate the two stimulus tones. The output levels of the two primary tones are calibrated using a "chirp". Figure 2.3 shows the frequency response of the chirp in a standard DB-100 (Zwislocki) coupler. Figure 2.4 is the frequency response of the chirp for two subjects, an adult and a Preterm (34-37 weeks) infant. This calibration shows the fit of the probe in the canal and the frequency response that the system is capable of based on the current position of the probe in the person's ear canal. This calibration is also used to zero the phase reference of the stimulus tone at the microphone where it sits in the ear canal.

Calibration of Phase Measurements

The output signals are generated in the ER-2 tubephone and sent down a 490 mm tube to the subject's ear canal. A sound which travels down a 490 mm tube from the speaker into an ear canal should have some differences in phase especially if there is also a large corresponding change in frequency from approximately 1.7 to 10 kHz. This situation was studied by changing the length of tubing of one of the tonal stimulators. A 270 mm length of tubing was added to the variable tone (f_1) transducer after the calibration

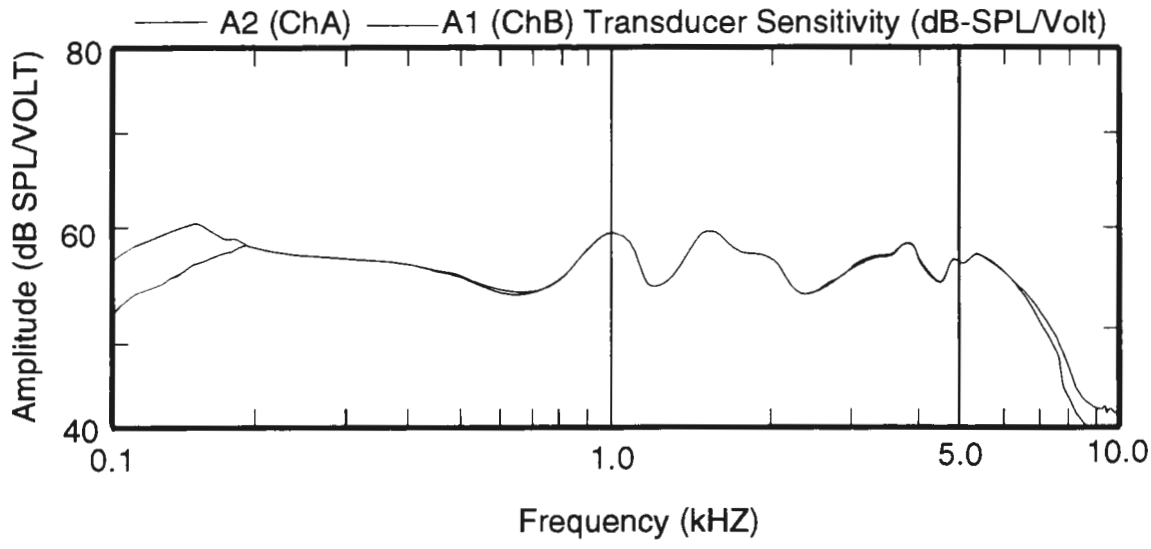


Figure 2.3 The frequency response in an adult ear canal simulator (DB-100 coupler) of the 1 volt chirp used in the calibration procedure.

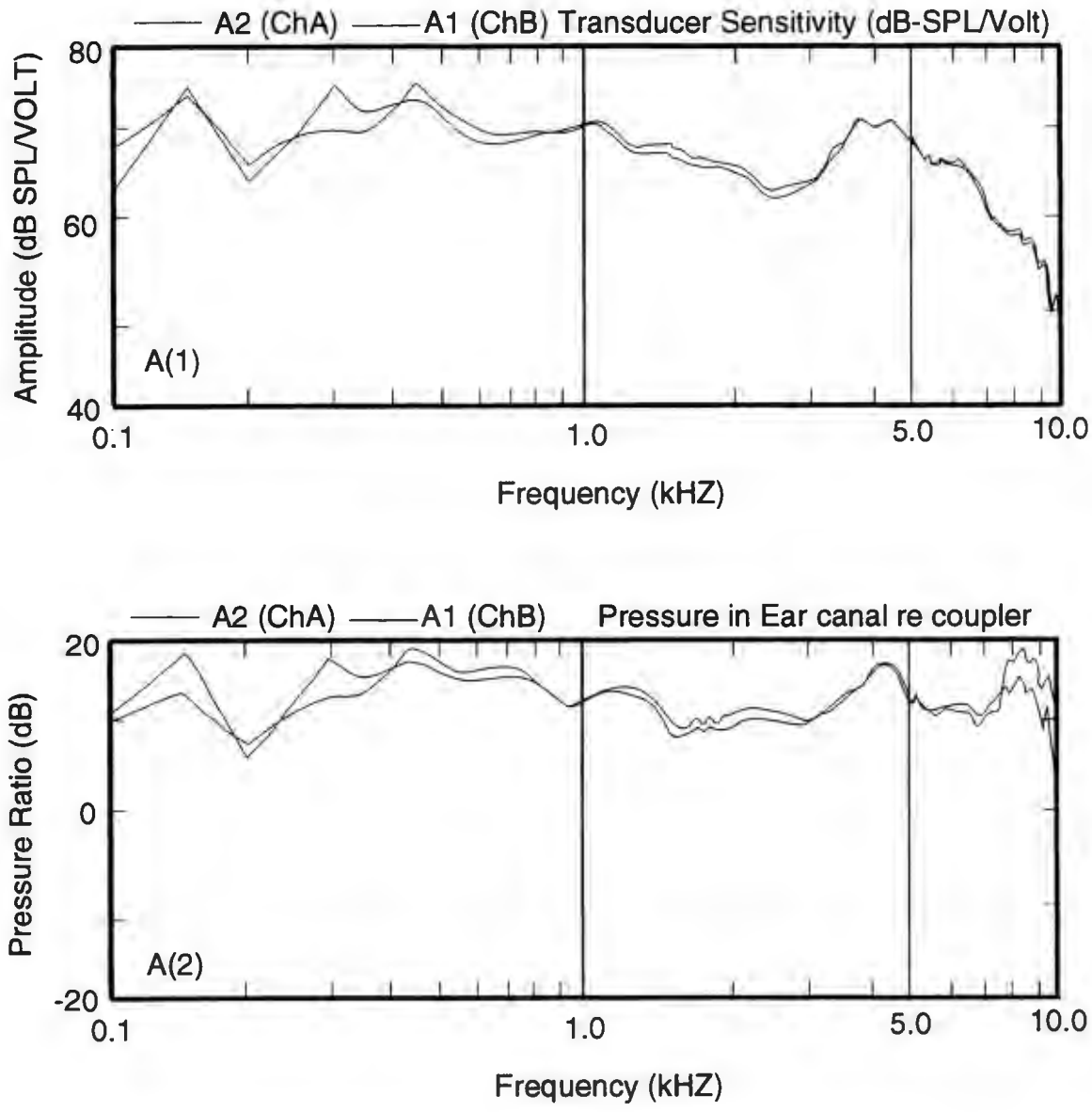


Figure 2.4 The frequency responses to the 1 volt chirp for both receivers in two subjects. (a) is from Subject NT (34-37 wks.) and (b) is from Subject SM (adult). The upper graphs are the responses to the chirp from both receivers. The lower graphs are the difference between the subject's ear canal response and that of the response from the standard DB-100 (Zwislocki) coupler.

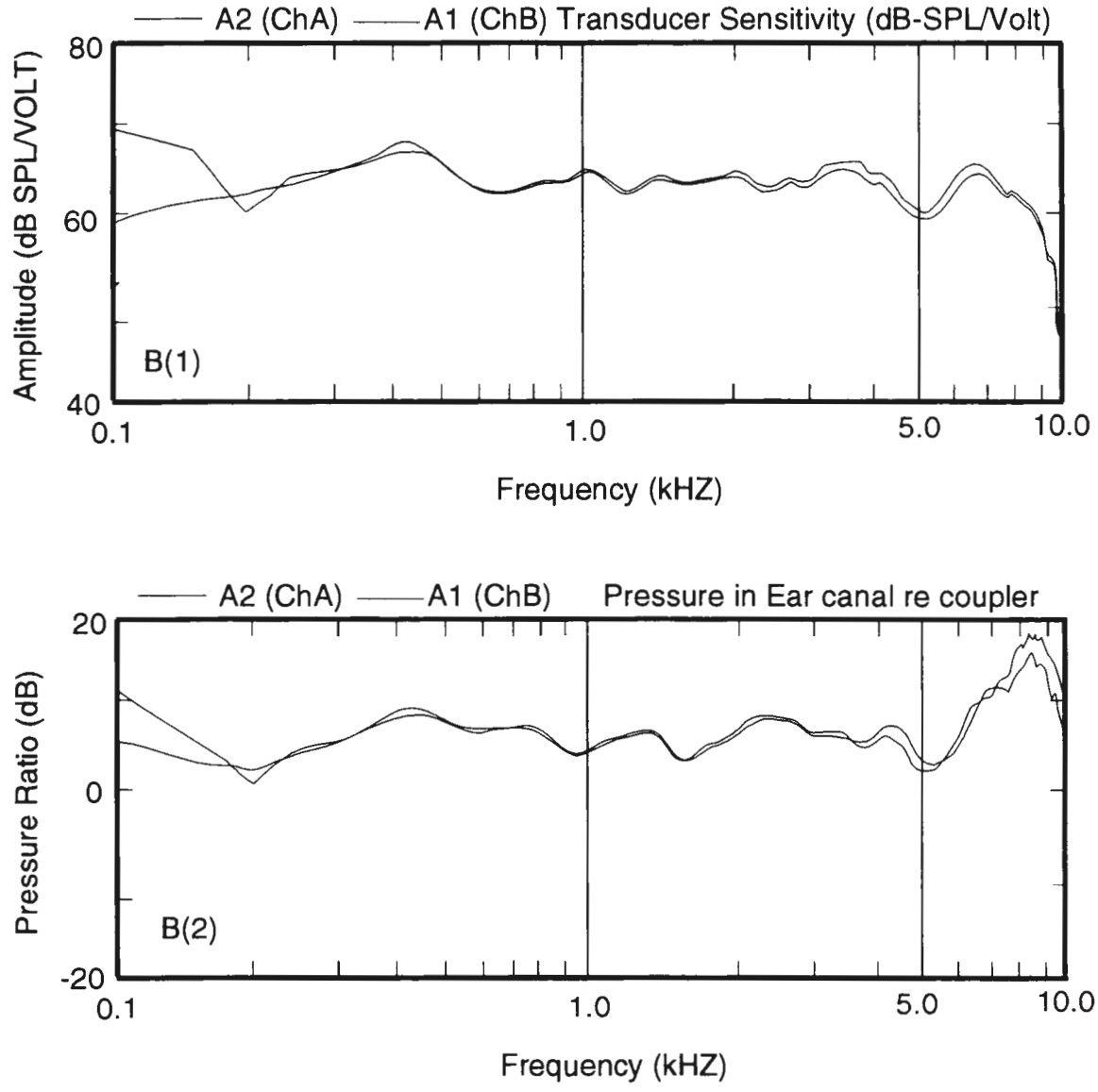


Figure 2.4 The frequency responses to the 1 volt chirp for both receivers in two subjects. (a) is from Subject NT (34-37 wks.) and (b) is from Subject SM (adult). The upper graphs are the responses to the chirp from both receivers. The lower graphs are the difference between the subject's ear canal response and that of the response from the standard DB-100 (Zwislocki) coupler.

procedure had occurred. Thus any change in phase of the variable tone would be due to the new tubing length and an additional delay would also correspond to this change in length.

$$\text{delay (ms)} = \frac{\text{length of tube (mm)}}{\text{speed of sound (mm/ms)}}$$

A 270 mm length of tubing added to the system would add a delay of 0.785 ms based on the speed of sound traveling through air being approximately 344 mm/ms. If the normal length of tubing is used and the phase for the f_1 frequencies measured in a 2 cc cavity the result, displayed in Figure 2.5, would be essentially a phase of zero for all $f_1$frequencies. Indeed, at most only a few degrees phase shift is observed. However, if additional tubing was added to the variable tone tube after the calibration and the phase of the tone was measured in the same 2cc cavity, the phase would be different than zero. The slopes for the phase of f_1 (associated with the six different f_2 frequency ranges) tones should reflect the change caused by the extra length of tubing. Figure 2.6 shows the slopes of the phase for the variable (f_1) tone for the six different f_2 frequencies. The delay caused by such a slope is calculated by:

$$\text{delay (ms)} = - \frac{\Delta\Psi}{360°} \bullet \frac{1}{\Delta f\ (\text{kHz})}$$

The delays associated with the six f_2 frequencies are shown in Table II.1: the mean delay is 0.801 ms. This result can be directly compared to the calculated delay caused by the additional length of tubing, which was 0.785 ms. Therefore, the calibration procedure largely corrects the phase measurement or calculates out the effect of the tubing length.

Frequency (Hz)	**Delay** (ms)
10009.8	.789
7031.3	.795
4931.6	.834
3466.8	.789
2441.4	.820
1709.0	.776

Table II.1 The delay caused by the extra tubing length at each f_2 frequency. Delays are for each of the f_2 frequencies for the f_1 phase. The mean delay is 0.801 ms.

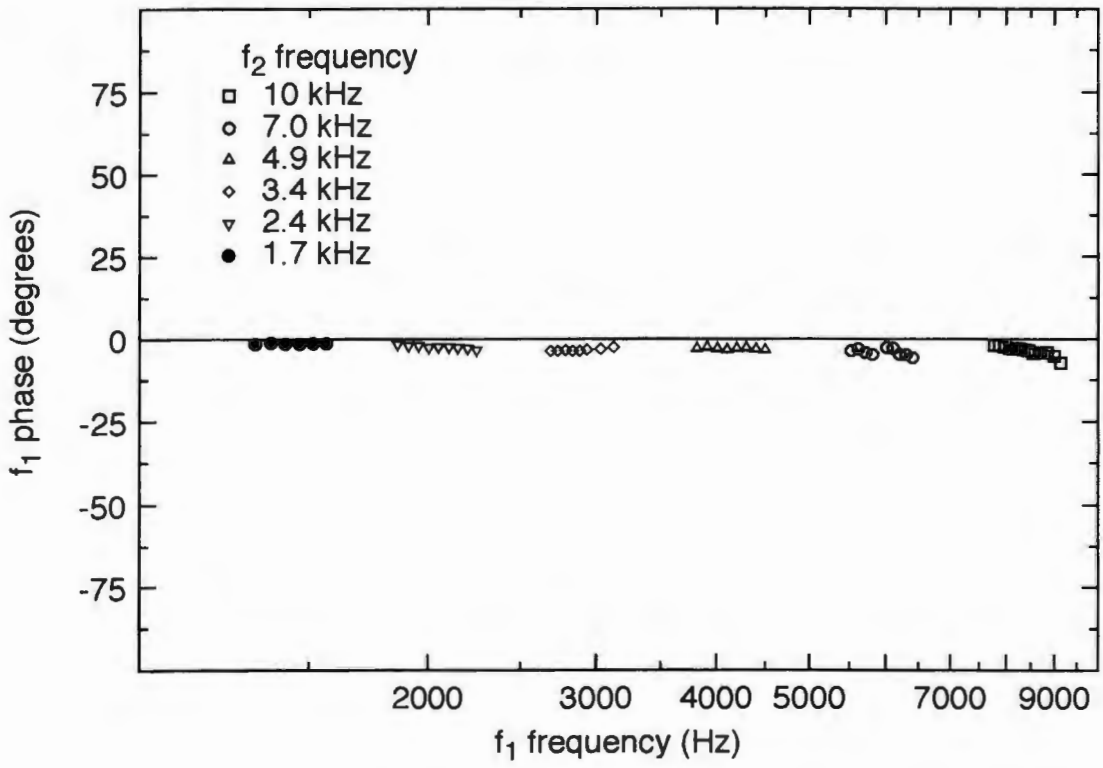


Figure 2.5 Phase plots by frequency from a 2cc cavity for a normal length ER-2 tubephone. Note that the phase is close to zero.

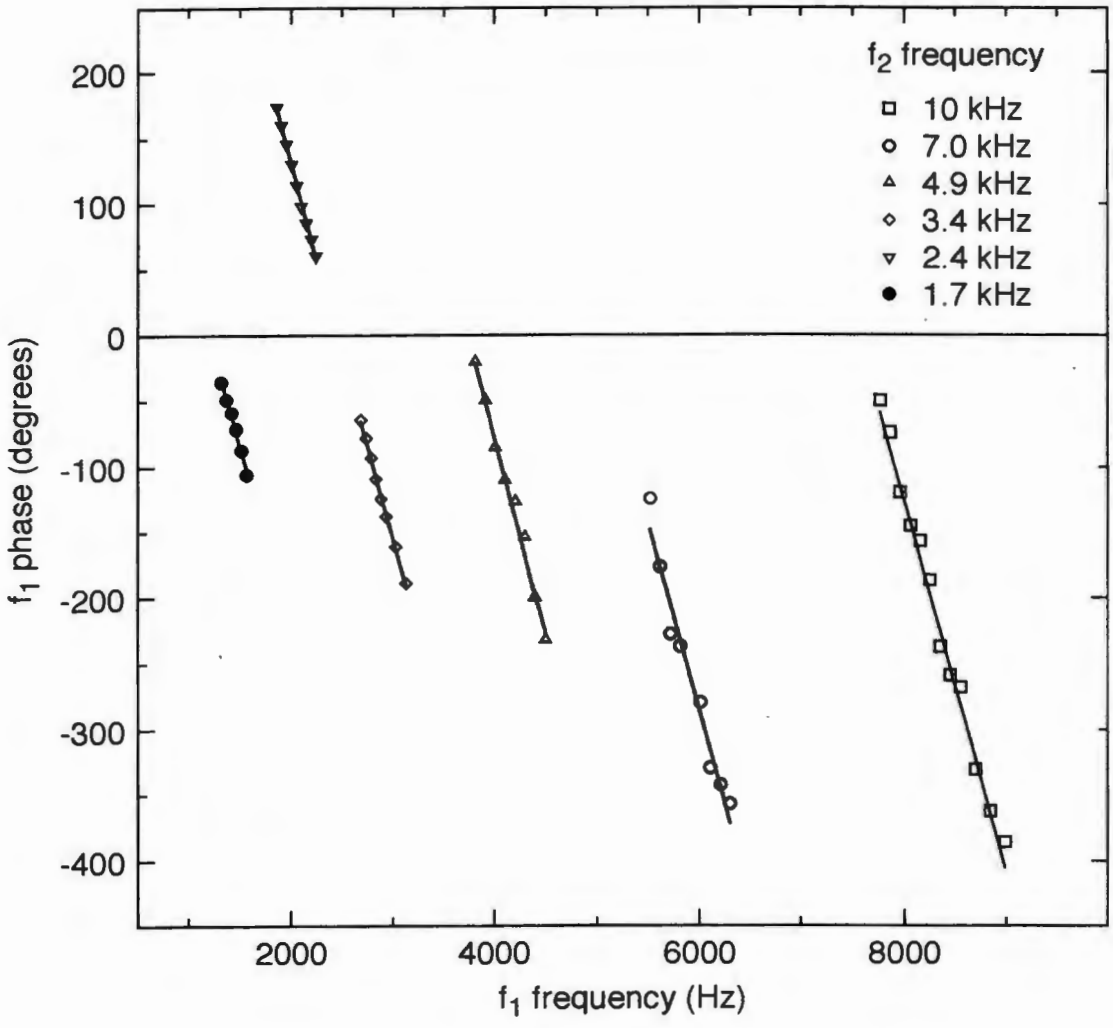


Figure 2.6 Phase plots generated in a 2 cc cavity from a probe that incorporates an additional length of tubing (270mm). Note the change in phase and the corresponding slope for the different f_2 frequencies from 1.7 to 10 kHz.

Location of Testing

Subjects were tested in one of three locations depending on the group to which they belonged. The Preterm groups were tested in either the Special Care Nursery (the step-down unit of the Neonatal Intensive Care Unit) or the Well-baby unit at the Foothills Hospital. The Term group was tested in the Well-baby nursery at the Foothills Hospital using a portable DPE unit. The adult group was tested at the Hearing Research Lab in the Heritage Medical Research Building using a stationary DPE unit. These units contained identical components (i.e. ER-10B and DSP board) except for the computer used to run the software.

The preterm neonates were tested in one of the units while they were sleeping or resting in their isolettes or bassinets. The term neonates were tested in their bassinets in a quiet room on the unit. The adults were tested while sitting comfortably in a sound-treated room (IAC #11-792).

SUBJECTS

Three hundred and forty-eight subjects were tested using DPEs and grouped into four groups according to age. It should be noted that more term born babies were tested and that the more premature the infant, the fewer numbers were available. This accounts for some of the difference between the number of infants tested and those used in this study. In addition, responses could not be recorded from a number of subjects due to excessive background noise, uncooperative subjects, middle ear problems and insufficient time to complete the testing. Only one ear was used from each subject as two ears from the same subject are highly correlated. Therefore each ear can not be treated as an independent random variable. Rosner (1982) reported that using standard methods of analysis with this type of data (i.e. two ears) results in p-values that are two to six times the nominal level.

As shown in Table II.2, the subjects within each group were matched for sex and consist of forty individuals each with the exception of the Group one. Group one, the youngest Preterm group with neonates 30 to 33 weeks CA, had only 25 subjects. The second is also a Preterm group but consists of neonates 34 to 37 weeks CA. Term infants between 38 and 42 weeks CA make up the third group. Both Preterm and Term babies were volunteered by their parents to participate in this study. The last was the adult group with ages between 16 and 41 years.

GROUP	AGE	TOTAL EARS TESTED		GENDER OF EARS USED		TOTAL EARS USED
		Male	Female	Male	Female	
1. Preterm (A)	30-33 weeks	18	14	15	10	25
2. Preterm (B)	34-37 weeks	37	44	20	20	40
3. Term	38-42 weeks	94	80	20	20	40
4. Adult	16-41 years	28	33	20	20	40
TOTAL		177	171			145

Table II.2 Number of ears tested and total ears used per group for the age studies.

Participants in these studies were screened using a DPE screening program, and only those with emissions received further testing. In addition, all adult subjects had hearing within normal limits (>20 dB HL) at .25, .5, 1, 2, 4, and 8 kHz. The mean and range of audiometric thresholds for adults ears are shown in Table II.3.

Threshold (dB SPL)	Frequency (Hz)						Age (years)
	250	500	1000	2000	4000	8000	
Intensity study							
mean	1.875	0.250	0.750	0.125	1.375	3.750	26.333
S. D.	4.895	5.424	4.465	5.487	5.309	7.316	4.527
Minimum	-5	-10	-10	-10	-5	-10	16
Maximum	15	15	10	15	10	20*	34
Age study							
mean	1.750	0.250	0.875	0.000	1.625	3.500	27.850
S. D.	5.256	4.662	3.560	5.064	4.442	7.355	5.713
Minimum	-10	-5	-10	-10	-5	-10	16
Maximum	15	10	10	15	10	20**	41

* 3 ears had thresholds > 15 dB SPL **2 ears had thresholds >15 dB SPL

Table II.3 Audiometric Thresholds and ages for all adult subjects.

DATA ANALYSIS

The DPE phase measurements were collected for each DPE frequency using the modified program 'CUBDISD'. It works by holding the probe (f_2) tone constant and moving the variable (f_1) tone around the probe tone. DPEs are recorded for a number of frequencies which are associated with the probe tone. The phase for these frequencies is also recorded, and plotted according to their probe frequency. However, a problem with phase wrapping occurs, especially in the high frequencies. The program computes the phase response of the DPE from the real and imaginary numbers generated from the Discrete Fast Fourier Transform (DFFT). The resulting phase response was based on a four quadrant arctangent function and therefore produced 2π phase discontinuities. An unwrapping procedure was applied to the response to eliminate this discontinuity and correct the phase angles by adding multiples of 2π, where needed, to smooth the transitions across branch cuts so that a continuous-phase curve could be obtained (Oppenheim & Schafer, 1989; MathWorks, 1990).

An example of phase unwrapping is shown in Figure 2.7. This Figure shows the phase results for subject RB (f_2 = 50 dB). Once the phase has been unwrapped, the slope for a set of phases which correspond to the f_2 frequency can be calculated. Some points may have to be removed from the analysis because they are contaminated or fall below the noise floor. The delay for the probe frequency was calculated from the slope (curve fit) and plotted in this Figure. The round-trip travel time associated with this f_2 = 10 kHz is 2.08 ms.

The resultant phase was plotted for their DPE frequency as a function of the associated f_2 frequency using Statview SE. A least squares regression line was fit to the phase response to generate a slope for each f_2 frequency. The round-trip travel time was calculated from the slope that is associated with the particular f_2 frequency:

$$\text{Round-trip travel time (ms)} = \frac{\Delta \text{Ø}}{360^\circ \bullet \Delta f \text{ (kHz)}}$$

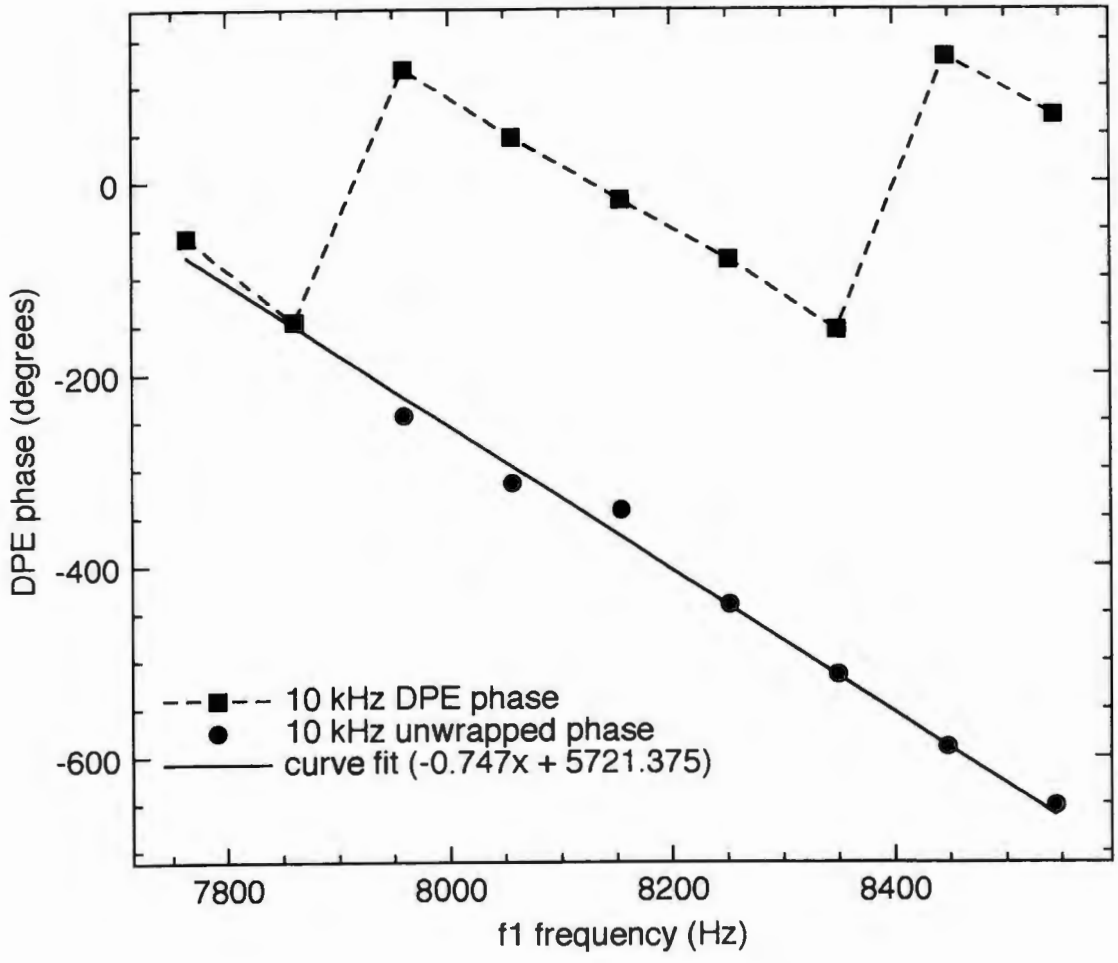


Figure 2.7 An example of phase unwrapping from Subject RB at f_2 = 50 dB. Note the abrupt upward shift in the wrapped phase responses (solid squares) at the third and eighth points. Unwrapping will make this a more linear function as shown in the solid circles. The curve fit associated with the unwrapped phase yielded a round-trip travel time for this frequency (f_2 = 10 kHz) of 2.08 ms.

Analysis of the data was done using Statview SE, Statview 4.01 and Superanova on different Macintosh computers. Statistical tests included Analysis of Variance, paired and unpaired t-Tests, and Regression Co-efficients. Any Post Hoc analysis used the Bonferroni-Dunn adjustment and the significance levels are noted with the corresponding analysis. The criterion for accepting statistical significance was $p < 0.01$ for all analysis.

Chapter 3. RESULTS

The Distortion Product Emission Phase-Frequency Relationship as a Function of Intensity in Adult Ears

Data were collected from 40 adults, one ear per subject, for f_2 intensity levels of 15-50 dB SPL in 5 dB steps. The intensity of the f_1 frequency was always 15 dB higher than the f_2 intensity. Figure 3.1 shows the levels of the DPE for all eight intensity combinations in one individual ear for a range of f_1 frequencies at each of the six fixed f_2 frequencies, together with the background noise level in the microphone. Results were obtained for 12 f_1 frequencies at the highest f_2 frequency (10 kHz) and for six f_1 frequencies at the lowest f_2 frequency (1.7 kHz). The DPE frequencies are plotted on a logarithmic scale, the level of the emissions in dB SPL. Each panel shows data for one fixed f_2 intensity; panel (a) presents data for the highest f_2 intensity, 50 dB, whereas in subsequent panels the f_2 intensity decreases by 5 dB. It is noted that the DPE amplitude decreases with decreasing stimulus level of the primary tones, whereas the level of the background noise stays fairly constant. In this Figure the optimum f_2/f_1 ratio, for largest emission, is also indicated; this will be discussed in more detail below. Note that the functions of DPE amplitude versus DPE frequency are fairly similar across intensity for fixed f_2 frequencies. Maximum DPE levels are about 25 dB SPL, for f_2 frequencies close to 10 kHz (Figure 3.1a,b) and the noise level stays between -30 to -20 dB SPL. For the two lowest intensity levels the DPEs are only occasionally above the noise level and this was consistent across subjects.

The percentage of subjects with detectable DPEs per f_2 frequency and intensity is shown in Figure 3.2. In general the optimum intensity levels appear to be 40 and 45 dB, both for lower and the one higher level, the percentage of subjects with emissions present decreases. There was no systematic dependence on f_2 frequency although for the highest intensities the percentage of emission decreases monotonically with frequency, i.e., there

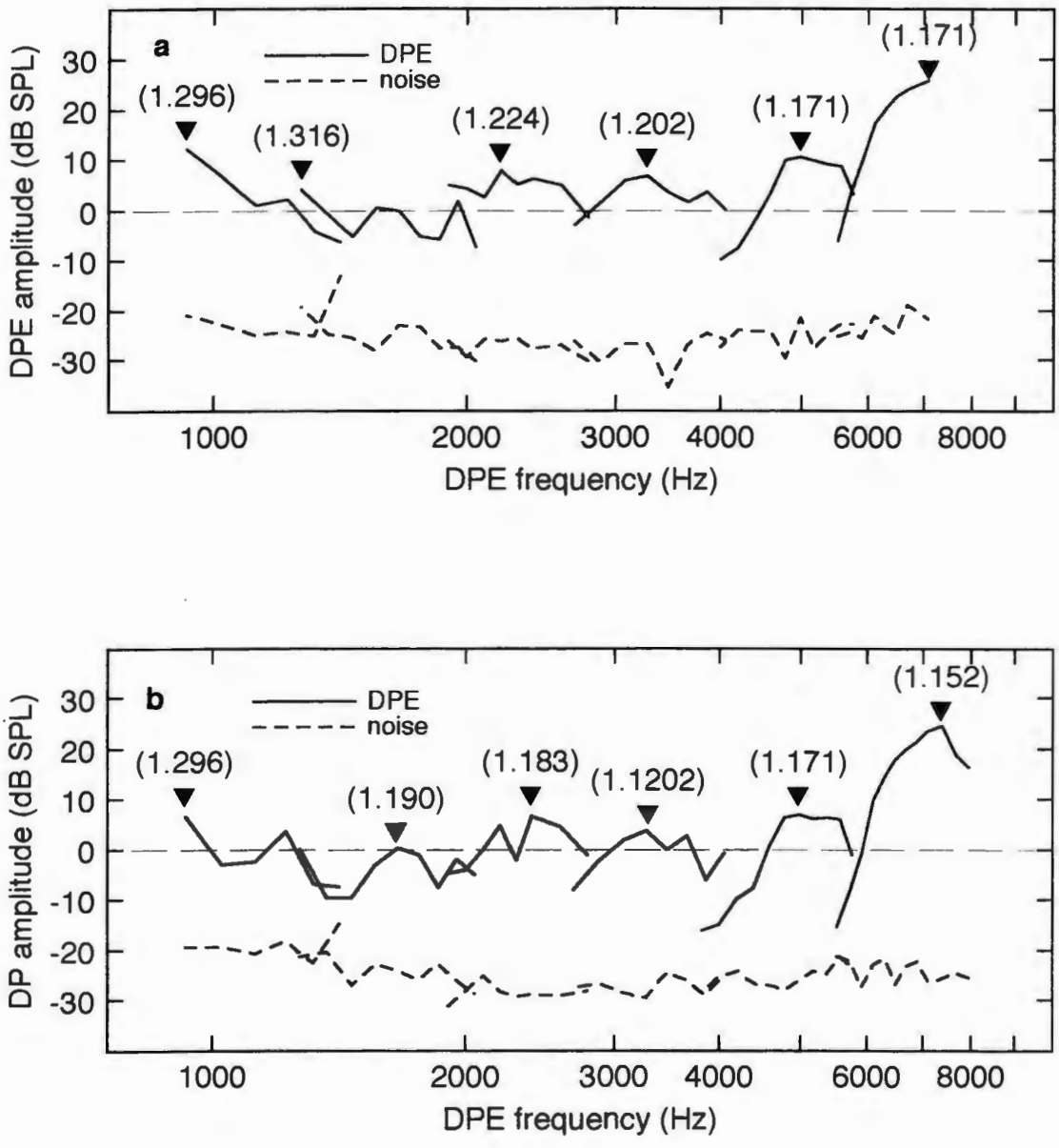


Figure 3.1 Emissions from a single adult subject (RB) for a f_1-sweep at different f_2 intensities: (a) 50 dB SPL, (b) 45 dB SPL, (c) 40 dB SPL, (d) 35 dB SPL, (e) 30 dB SPL, (f) 25 dB SPL, (g) 20 dB SPL and (h) 15 dB SPL. These eight intensity combinations are for a range of f_1 frequencies at each of the six fixed f_2 frequencies. This resulted in 12 f_1 frequencies at the highest f_2 frequency (10 kHz) and six f_1 frequencies at the lowest f_2 frequency (1.7 kHz). Optimum f_2/f_1 ratios are shown in brackets above each trace.

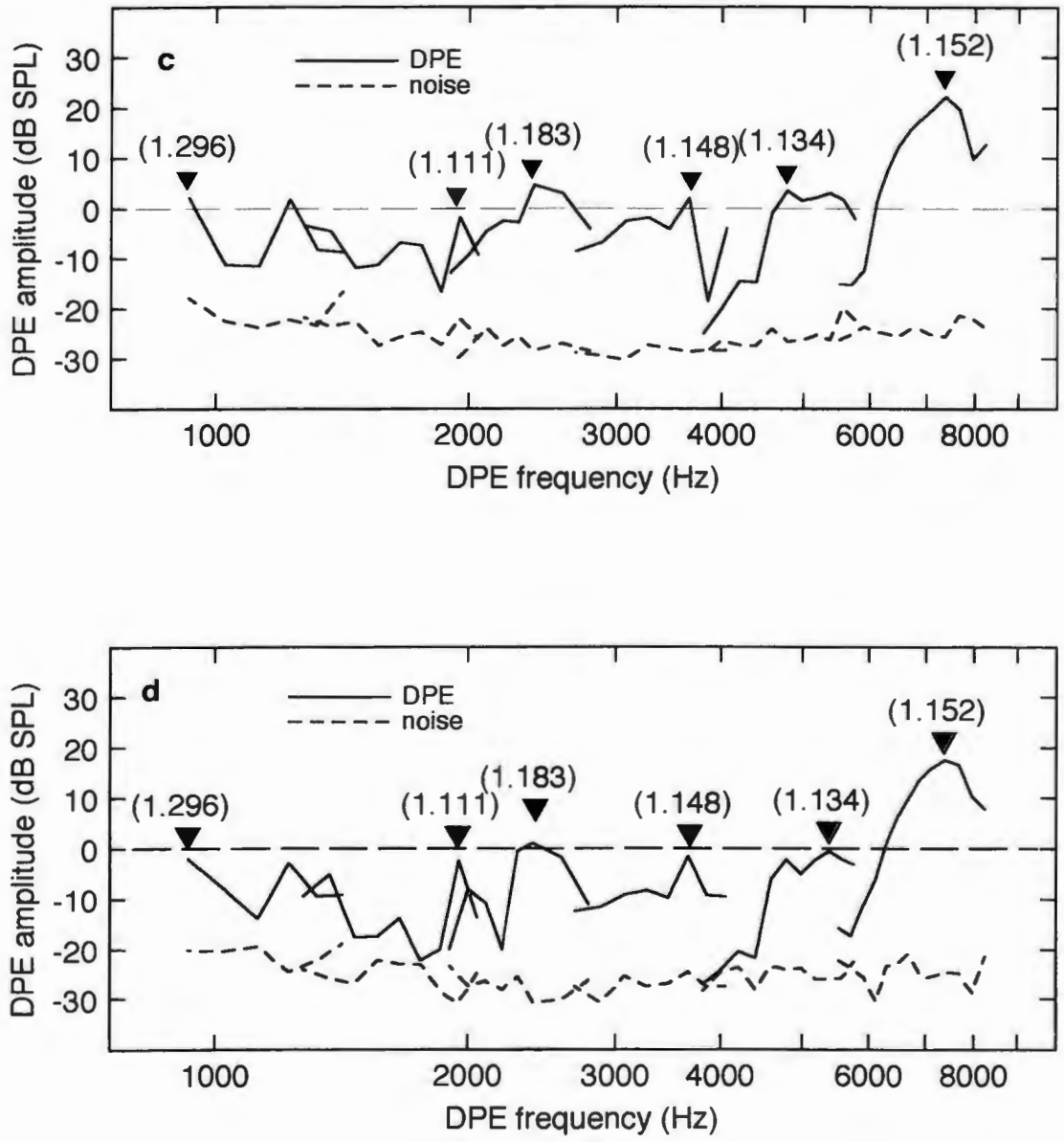


Figure 3.1 Emissions from a single adult subject (RB) for a f_1-sweep at different f_2 intensities: (a) 50 dB SPL, (b) 45 dB SPL, (c) 40 dB SPL, (d) 35 dB SPL, (e) 30 dB SPL, (f) 25 dB SPL, (g) 20 dB SPL and (h) 15 dB SPL. These eight intensity combinations are for a range of f_1 frequencies at each of the six fixed f_2 frequencies. This resulted in 12 f_1 frequencies at the highest f_2 frequency (10 kHz) and six f_1 frequencies at the lowest f_2 frequency (1.7 kHz). Optimum f_2/f_1 ratios are shown in brackets above each trace.

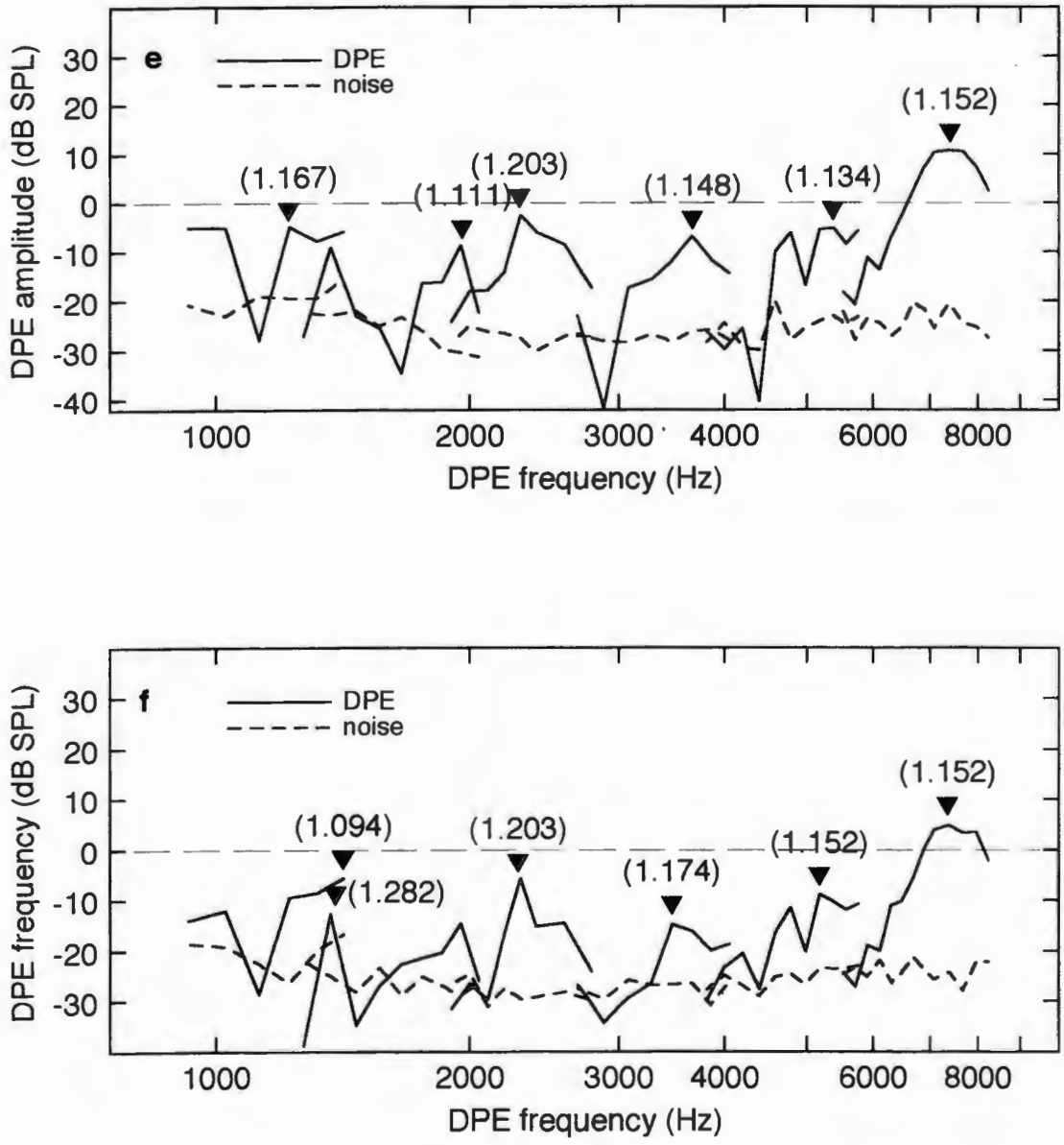


Figure 3.1 Emissions from a single adult subject (RB) for a f_1-sweep at different f_2 intensities: (a) 50 dB SPL, (b) 45 dB SPL, (c) 40 dB SPL, (d) 35 dB SPL, (e) 30 dB SPL, (f) 25 dB SPL, (g) 20 dB SPL and (h) 15 dB SPL. These eight intensity combinations are for a range of f_1 frequencies at each of the six fixed f_2 frequencies. This resulted in 12 f_1 frequencies at the highest f_2 frequency (10 kHz) and six f_1 frequencies at the lowest f_2 frequency (1.7 kHz). Optimum f_2/f_1 ratios are shown in brackets above each trace.

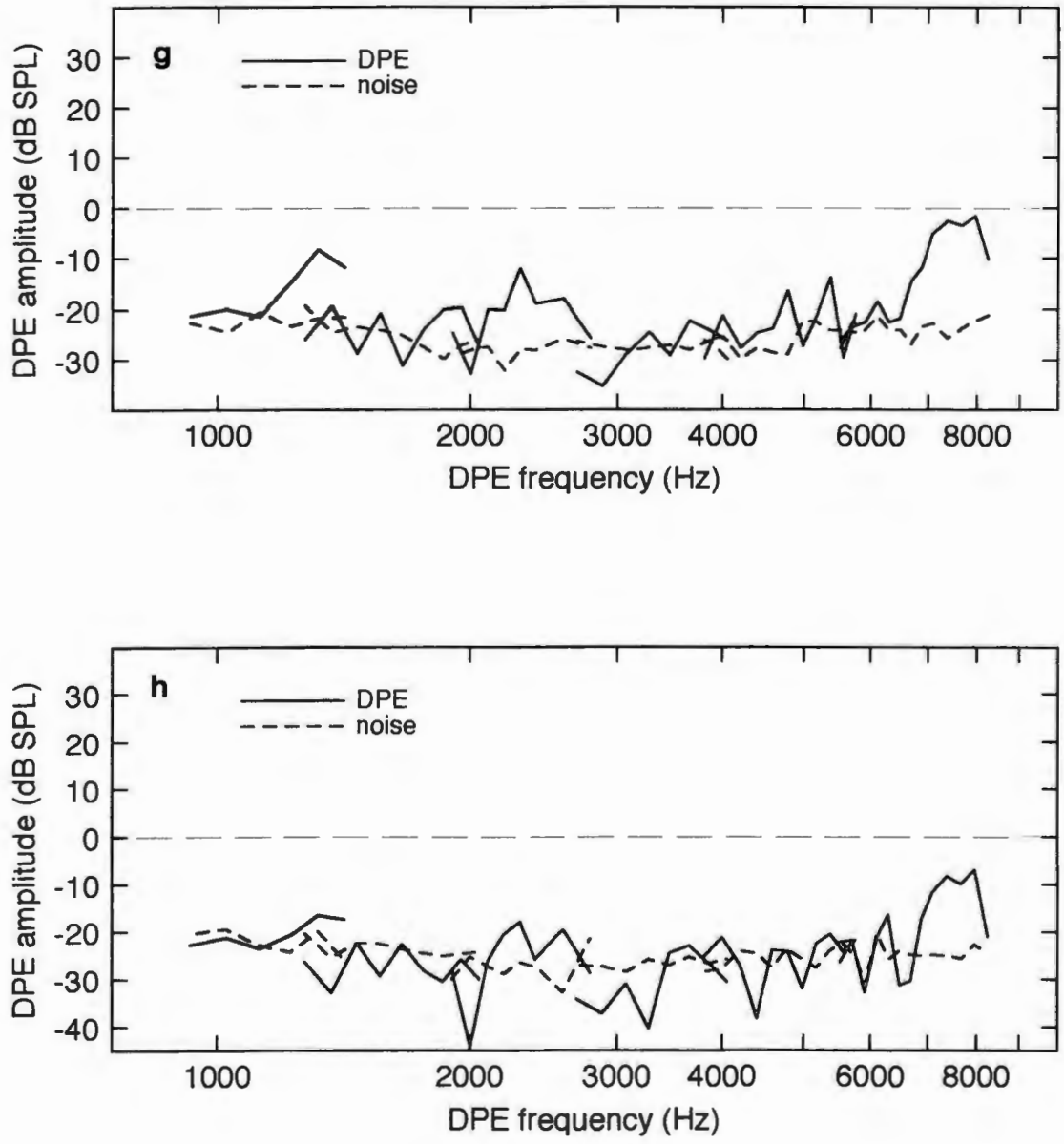


Figure 3.1 Emissions from a single adult subject (RB) for a f_1-sweep at different f_2 intensities: (a) 50 dB SPL, (b) 45 dB SPL, (c) 40 dB SPL, (d) 35 dB SPL, (e) 30 dB SPL, (f) 25 dB SPL, (g) 20 dB SPL and (h) 15 dB SPL. These eight intensity combinations are for a range of f_1 frequencies at each of the six fixed f_2 frequencies. This resulted in 12 f_1 frequencies at the highest f_2 frequency (10 kHz) and six f_1 frequencies at the lowest f_2 frequency (1.7 kHz). Optimum f_2/f_1 ratios are shown in brackets above each trace.

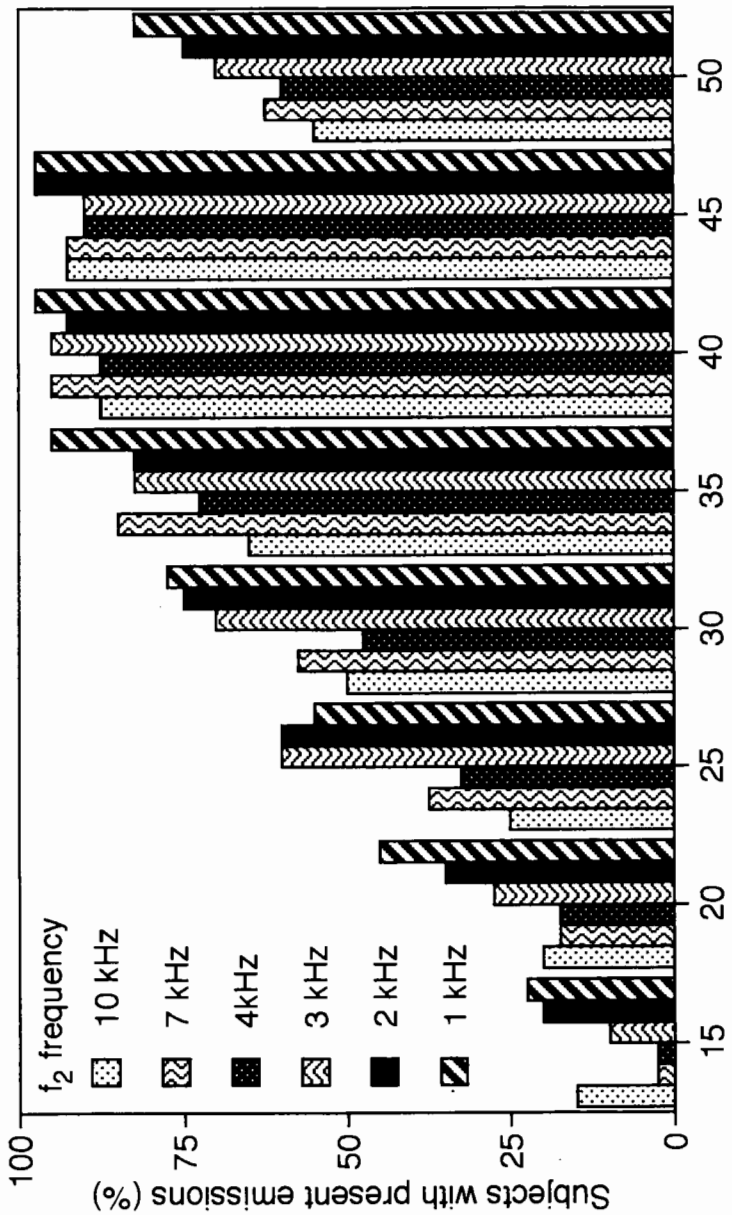


Figure 3.2 Percentage of subjects with present emissions for different f_2 intensity levels.

were more emissions at lower frequencies. At the two lowest intensities the percentage of emissions present was relatively low, therefore these intensities were eliminated from further analysis.

After the emission data were collected the phase of each DPE was plotted as a function of DPE frequency, a phase unwrapping algorithm was used to obtain a uniformly decreasing phase-frequency relationship. All phase-frequency curves were inspected for accurate phase unwrapping. An example of such a phase-frequency relationship for the ear shown in Figure 3.1 for an f_2 intensity of 50 dB were shown in Figure 3.3.

The round-trip travel times estimated from the phase measurements of each f_2 intensity level for this subject are shown in Figure 3.4. The round-trip travel time at each intensity level is compared to the mean round-trip travel time.

Figure 3.5 shows the round-trip travel times for all individual subjects for the six f_2-intensities used as a function of f_2 frequency. A double logarithmic scale is used and the power function curve fits are drawn in. Figure 3.5(a), shows results for an f_2-intensity of 50 dB, subsequent panels show data for decreasing f_2-intensities. The collection of power function curve fits for the six intensities are presented in Figure 3.6, and one can see that the curves are not completely parallel. In fact there was a tendency for the curves to become steeper for lower intensity levels. This is further illustrated in Figure 3.7 where the exponents of the power functions, representing the slope of the functions in a log-log plot, are plotted as a function of f_2 level. A linear regression line was fit through the data points and the slope of that line appeared to be significantly different from zero (Table III.1).

Regression Coefficients
exponent vs. intensity

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	-.979	.038	-.979	-25.632	<.0001
intensity	5.646E-3	7.184E-4	.969	7.859	.0014

Table III.1 The Linear regression exponents are significantly different from zero.

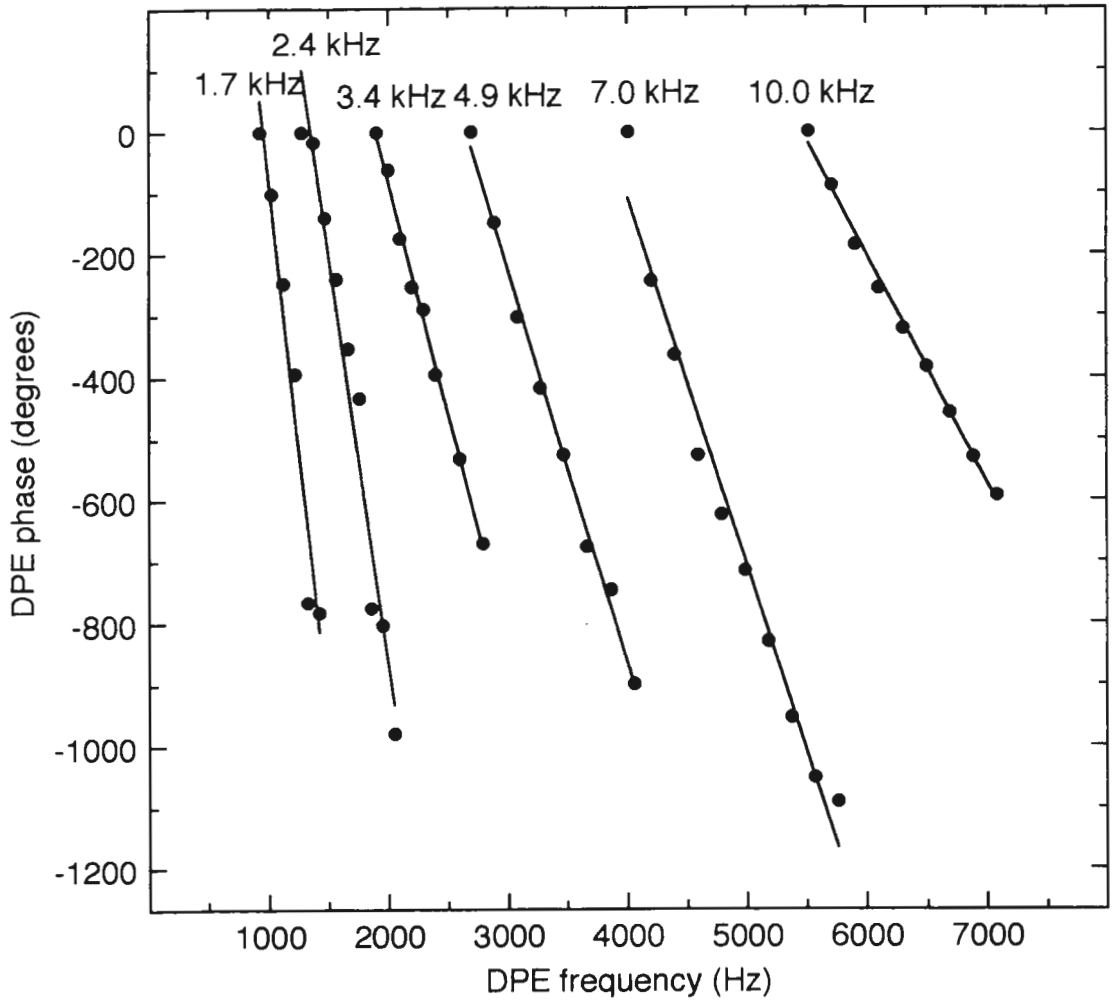


Figure 3.3 Unwrapped DPE phase values plotted for their DPE frequencies for subject RB. Power functions for each f_2 frequency are shown.

Figure 3.4 An example of round-trip travel times for six f_2 intensities from a single subject (RB). These travel-times are compared to the mean round-trip travel time for the adult group at each of the f_2 intensities.

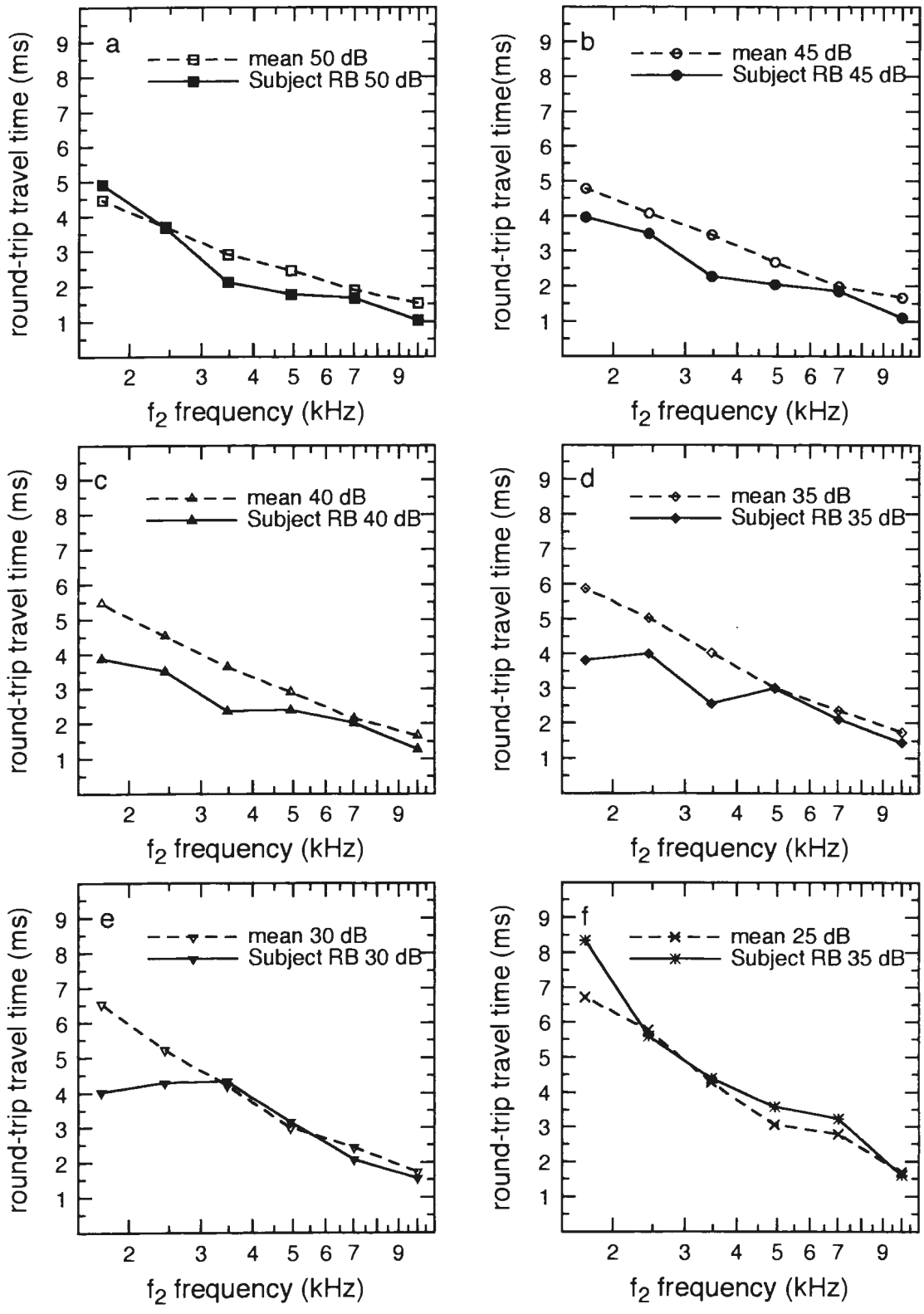

a
mean 50 dB
Subject RB 50 dB
b
mean 45 dB
Subject RB 45 dB
c
mean 40 dB
Subject RB 40 dB
d
mean 35 dB
Subject RB 35 dB
e
mean 30 dB
Subject RB 30 dB
f
mean 25 dB
Subject RB 35 dB
round-trip travel time (ms)
round-trip travel time(ms)
f2 frequency (kHz)

Figure 3.4

Figure 3.5 Power functions for the round-trip travel times for the f_2 intensity series as fit to the data from each of the six different f_2 intensities.

Figure 3.5

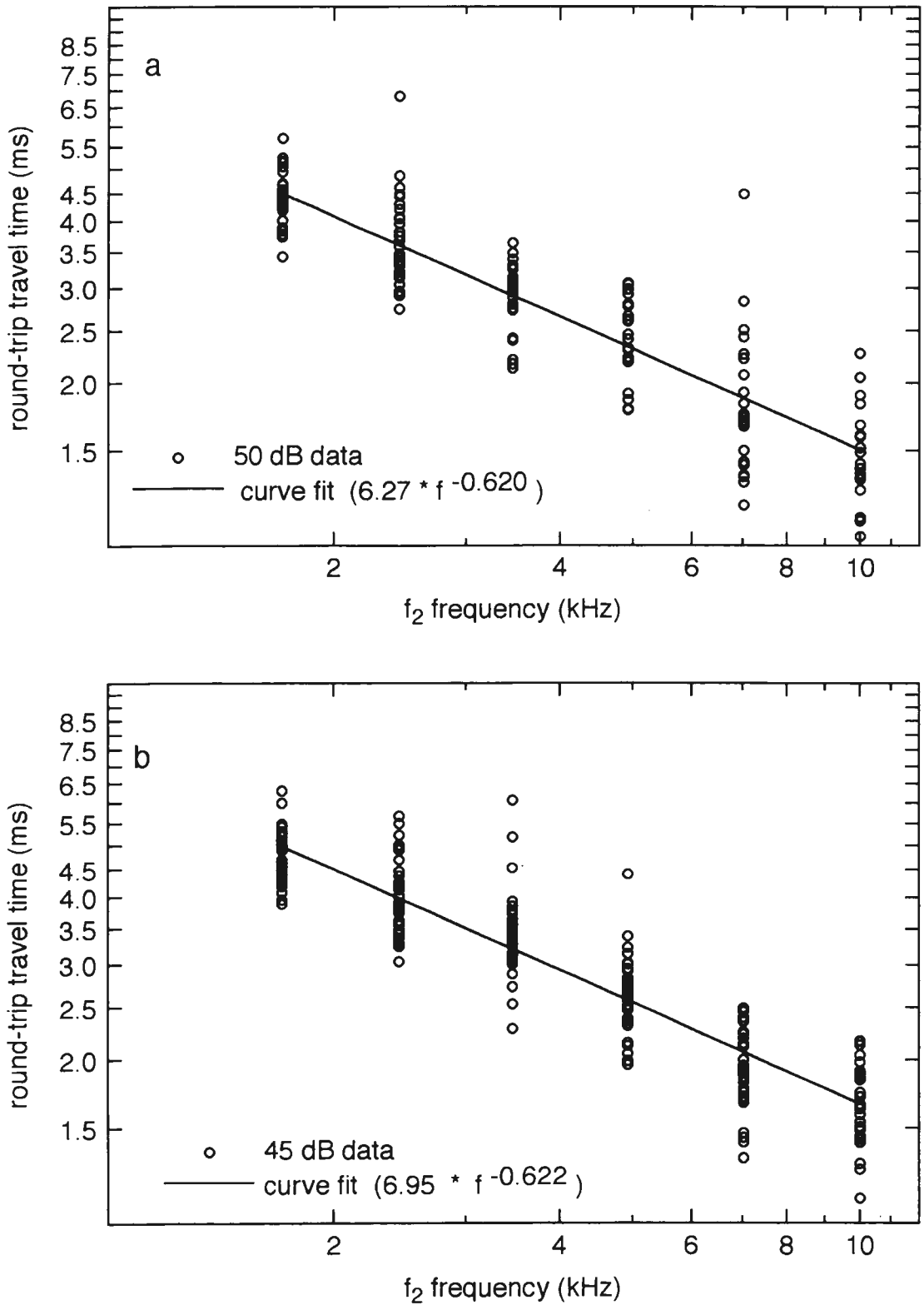
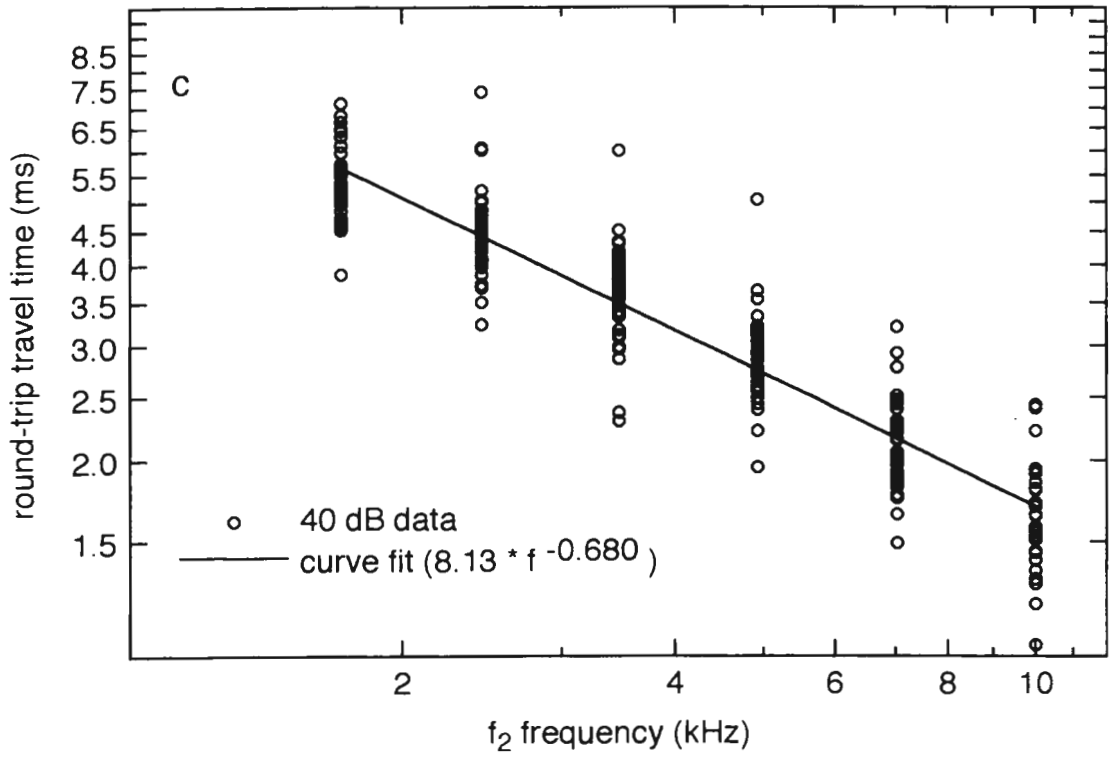

a
round-trip travel time (ms)
8.5
7.5
6.5
5.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
50 dB data
curve fit (6.27 * f -0.620)
2
4
6
8
10
f2 frequency (kHz)
b
round-trip travel time (ms)
45 dB data
curve fit (6.95 * f -0.622)
f2 frequency (kHz)

Figure 3.5


c
round-trip travel time (ms)
8.5
7.5
6.5
5.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
40 dB data
curve fit (8.13 * f -0.680)
2
4
6
8
10
f2 frequency (kHz)

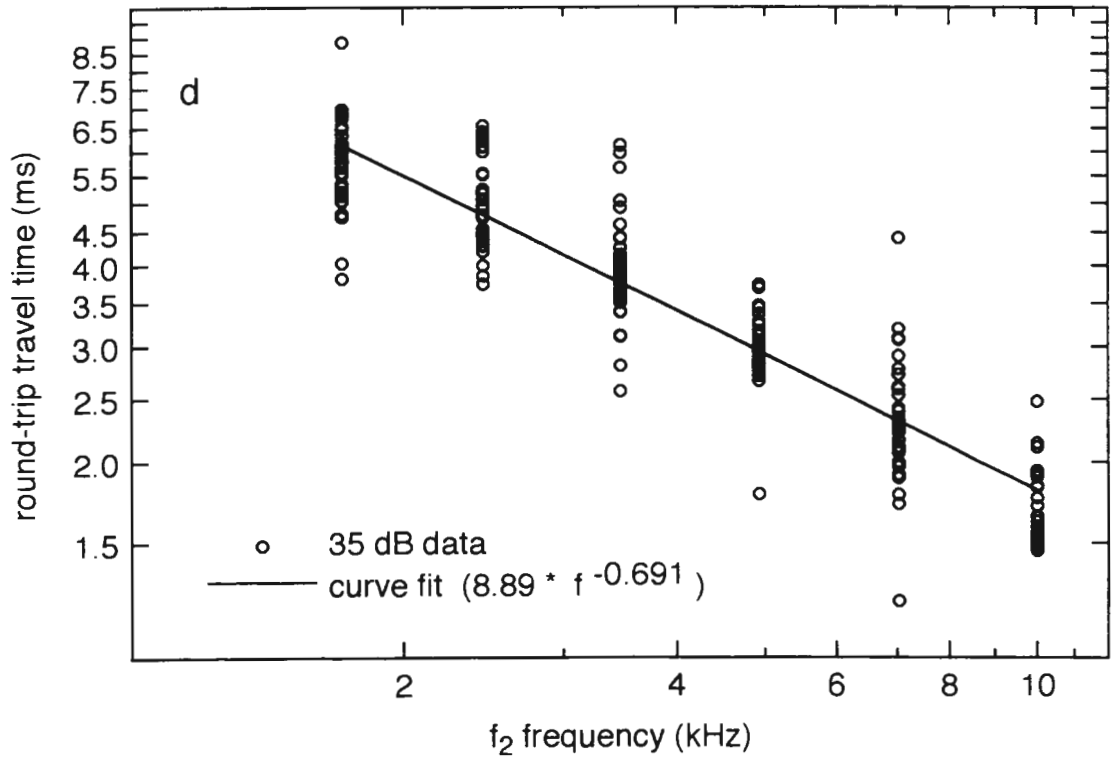
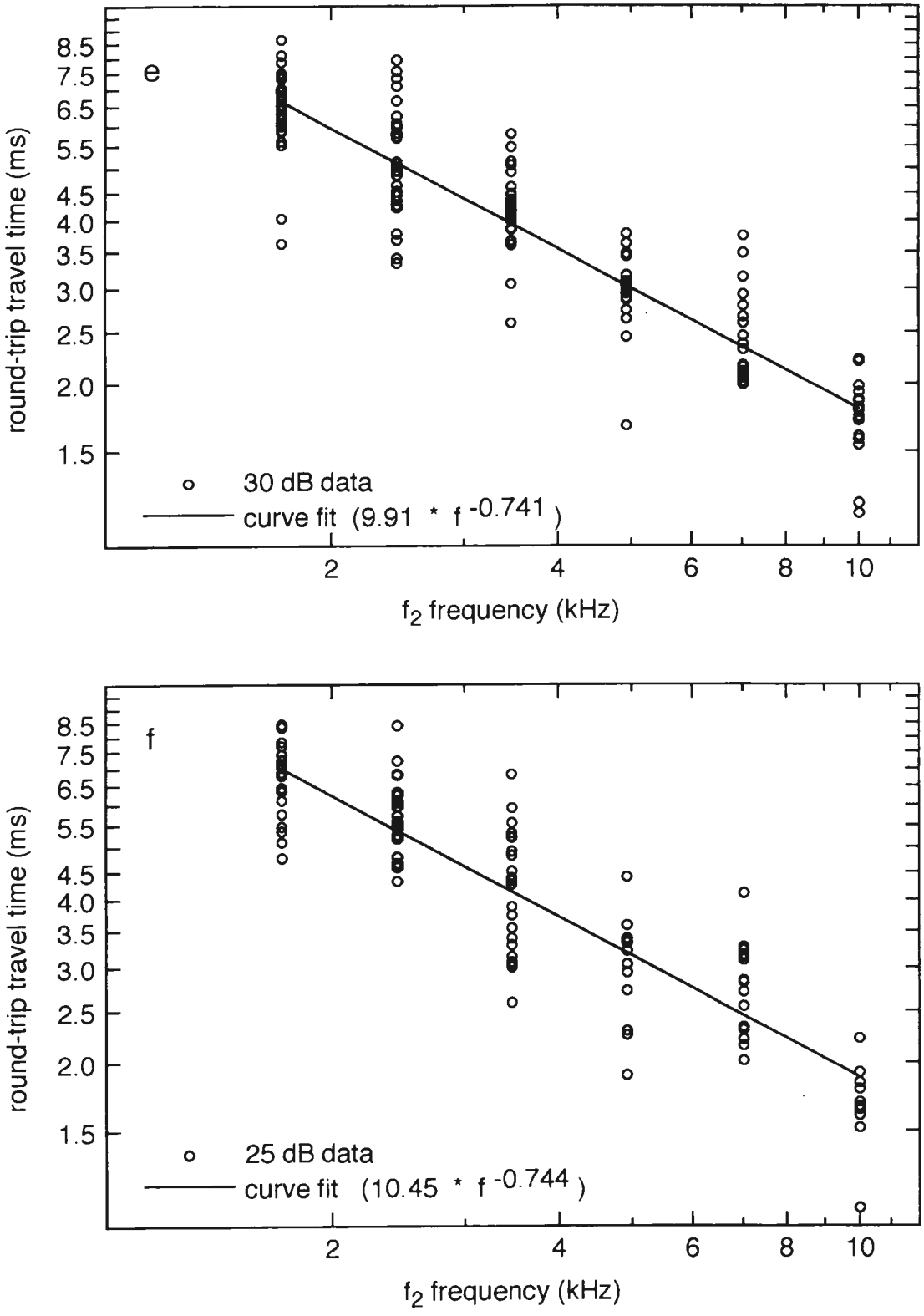

d
round-trip travel time (ms)
8.5
7.5
6.5
5.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
35 dB data
curve fit (8.89 * f -0.691)
2
4
6
8
10
f2 frequency (kHz)

Figure 3.5


e
round-trip travel time (ms)
8.5
7.5
6.5
5.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
30 dB data
curve fit (9.91 * f -0.741)
2
4
6
8
10
f2 frequency (kHz)
f
round-trip travel time (ms)
25 dB data
curve fit (10.45 * f -0.744)
f2 frequency (kHz)

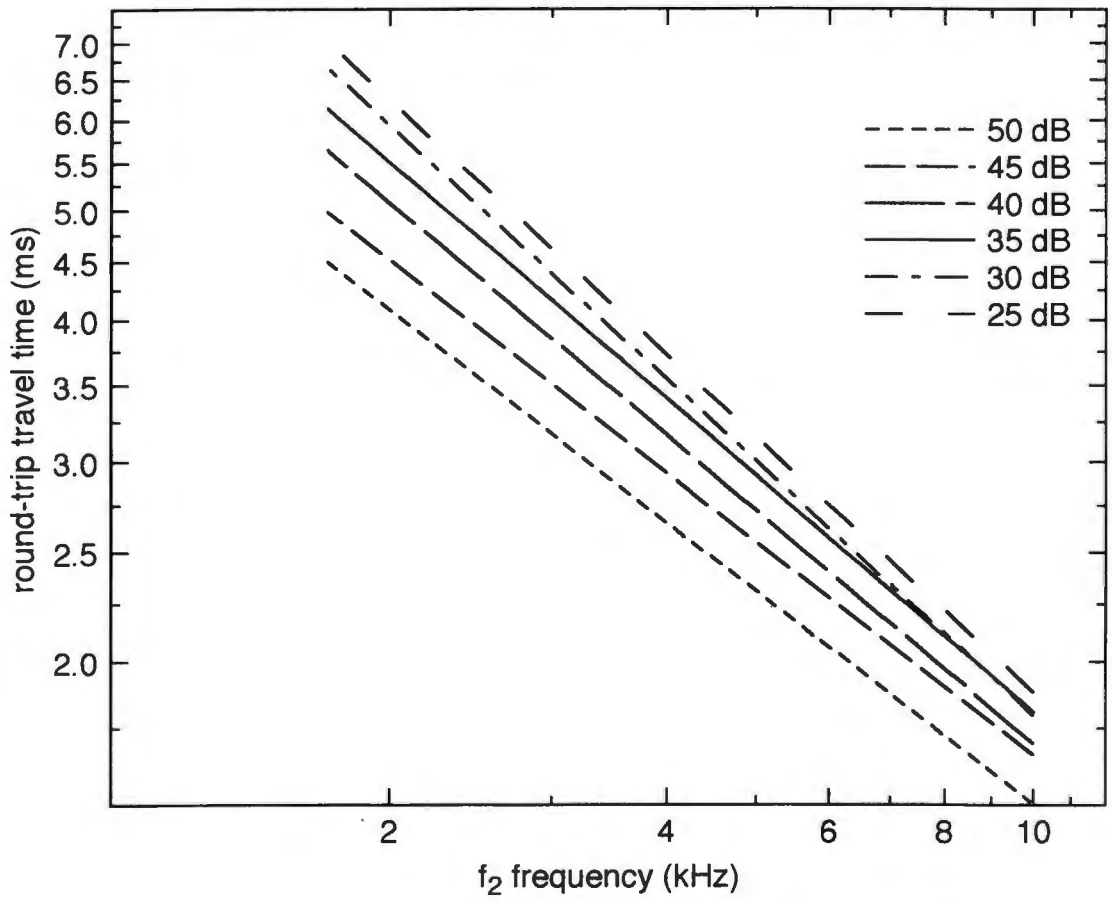


Figure 3.6 Dependence of exponents on f_2 intensity level with linear regression line draw in.

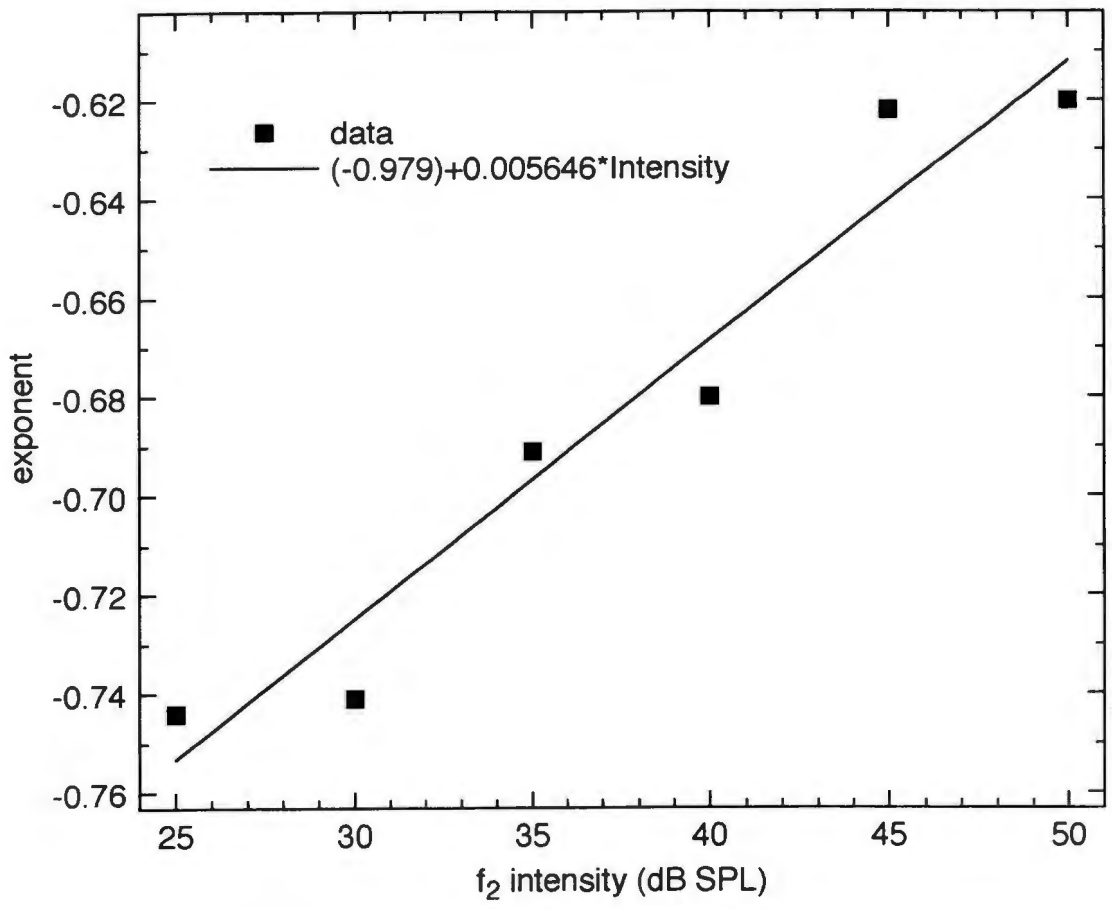


Figure 3.7 Slope of the linear regression is significantly different from zero. The exponents are from the slopes of the linear regression lines for the different f_2 intensities as shown in Figure 3.5.

The Age Dependence of the Round-Trip Travel Time

The age dependence of the DPE phase-frequency relationship, which gives the round-trip travel times, was studied in four different age groups. Three newborn groups were used: 30-33 weeks CA, 34-37 weeks CA and 38-42 weeks CA (term). For comparison an adult group, different from the one presented in the previous section (as indicated in the Methods section), was used. A total of 145 ears were tested in the four groups; 25 ears in the 30-33 week olds, 40 ears in the 34-37 week olds, 40 ears in the 38-42 week group and 40 ears in the adult group. The intensity levels used were constant with f_2=45 dB SPL and f_1=60 dB SPL, the optimum levels for detectability in the adult group.

An example of emission amplitudes and background noise for subjects from each of the four age groups is shown in Figure 3.8. Panel (a) shows data for a subject from the youngest age group, panel (b) from the 34-37 week olds, panel (c) from the 38-42 week olds and panel (d) from the adult group. One notices that in general the emission strength was larger for the younger subjects and that the noise floor, especially at the lower frequencies, was substantially higher in the newborns. This is the result of testing in the neonatal intensive care unit whereas the adults were tested in a sound treated room. Again DPE amplitude is plotted in dB SPL and the DPE frequency is shown on a logarithmic scale.

Figure 3.9 shows for each of these subjects the phase-frequency relationship using a logarithmic frequency axis; one notes that the linear regression lines become curved in such a representation. The individual subject's round-trip travel time was computed from these phase-frequency functions and compared to the mean group round-trip travel time. For each subject one panel shows the phase-frequency curves and the other panel the comparison between the individual travel time and the mean group travel time. One notices a generally monotonic decrease in round-trip travel time with increasing f_2 frequency.

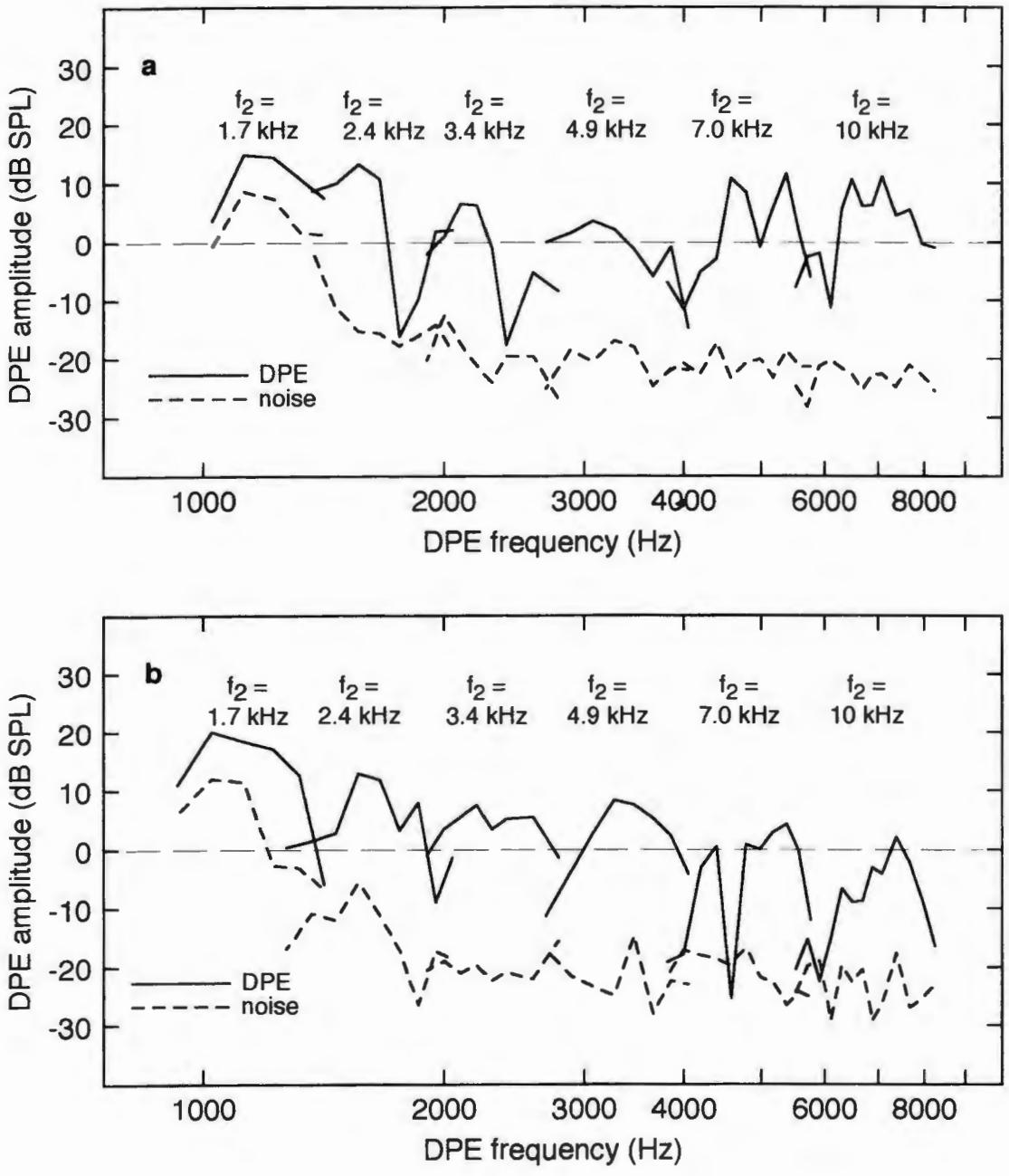


Figure 3.8 Examples of emissions from a subject in each group at a f_2 intensity of 45 dB SPL. Panel (a) is from Group 1 (30-33 wks.), Panel (b) is from Group 2 (34-37 wks.), Panel (c) is from Group 3 (38-42 wks.) and Panel (d) is from Group 4 (Adult). The solid line is the DPE amplitude and the dashed line is the noise floor. The noise floor rises in the low frequencies for the term (c) and preterm (a,b) groups but not in the adult group.

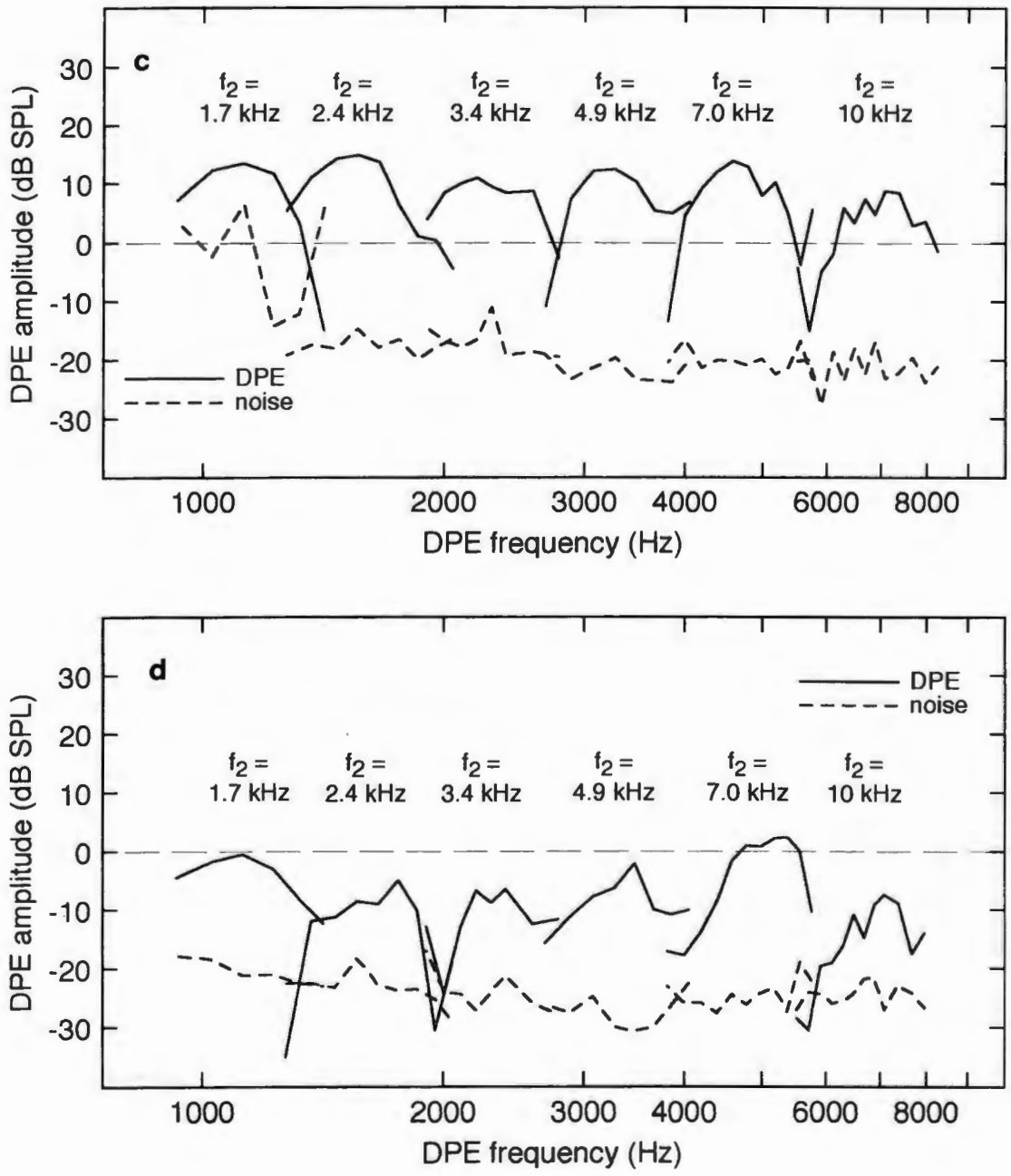


Figure 3.8 Examples of emissions from a subject in each group at a f_2 intensity of 45 dB SPL. Panel (a) is from Group 1 (30-33 wks.), Panel (b) is from Group 2 (34-37 wks.), Panel (c) is from Group 3 (38-42 wks.) and Panel (d) is from Group 4 (Adult). The solid line is the DPE amplitude and the dashed line is the noise floor. The noise floor rises in the low frequencies for the term (c) and preterm (a,b) groups but not in the adult group.

Figure 3.9 Results from the individual data from Figure 3.8. Panels (a), (c), (e), & (g) are examples of the phase results and the slopes for a subject from each group. Panels (b), (d), (f) & (h) are the round-trip travel times for the same subject and the mean travel time for each group. Panels (a) and (b) are from Group 1 (30-33 wks.), (c) and (d) are from Group 2 (34-37 wks.), (e) and (f) are from Group 3 (38-42 wks.), and (g) and (h) are from Group 4 (Adult). Note: because of the logarithmic frequency scale the linear regression lines in (a), (c), (e) and (g) do not appear as straight lines.

Figure 3.9

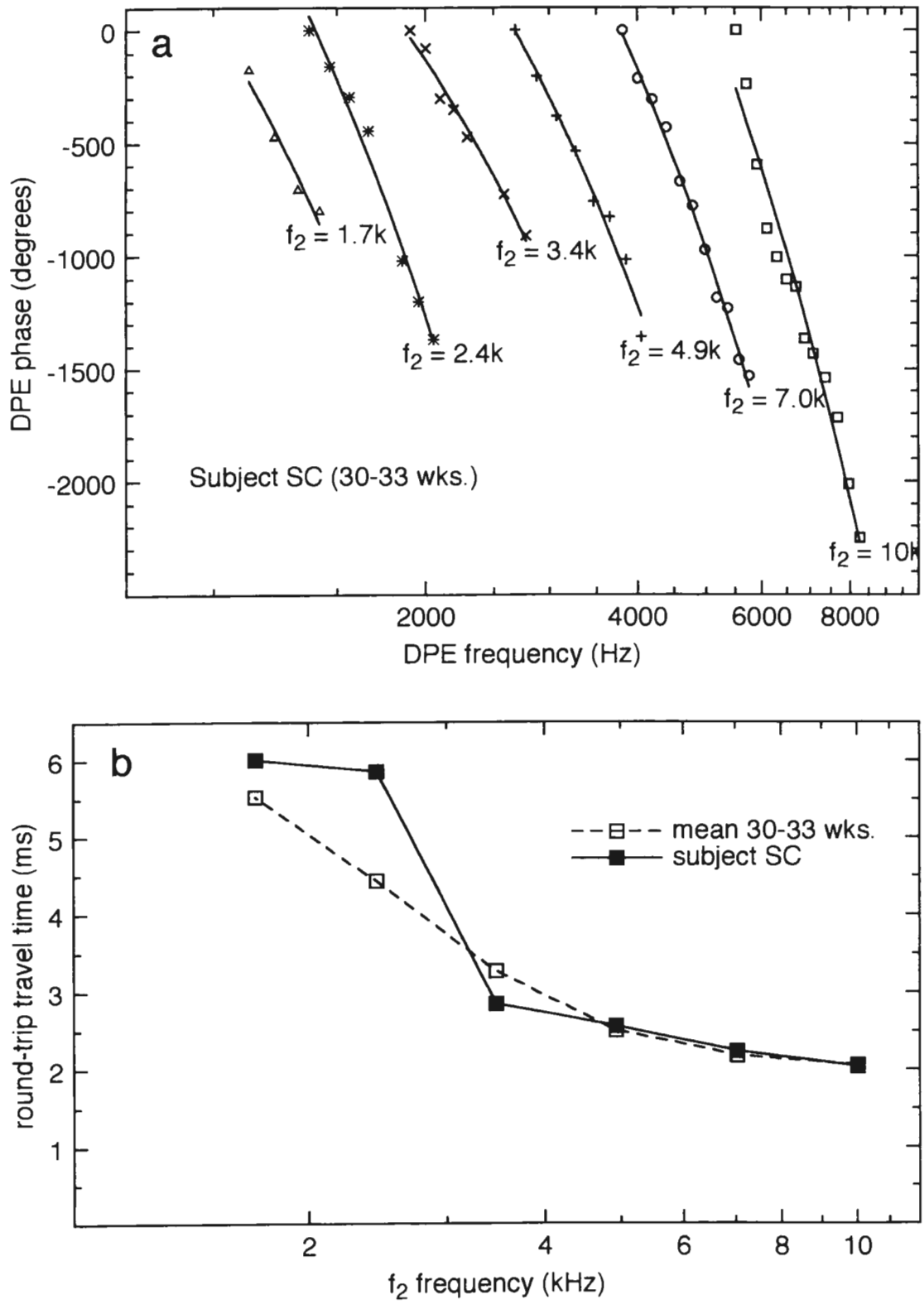

a
0
-500
-1000
-1500
-2000
DPE phase (degrees)
f_2 = 1.7k
f_2 = 2.4k
f_2 = 3.4k
f_2 = 4.9k
f_2 = 7.0k
f_2 = 10k
Subject SC (30-33 wks.)
2000
4000
6000
8000
DPE frequency (Hz)
b
6
5
4
3
2
1
round-trip travel time (ms)
mean 30-33 wks.
subject SC
2
4
6
8
10
f_2 frequency (kHz)

Figure 3.9

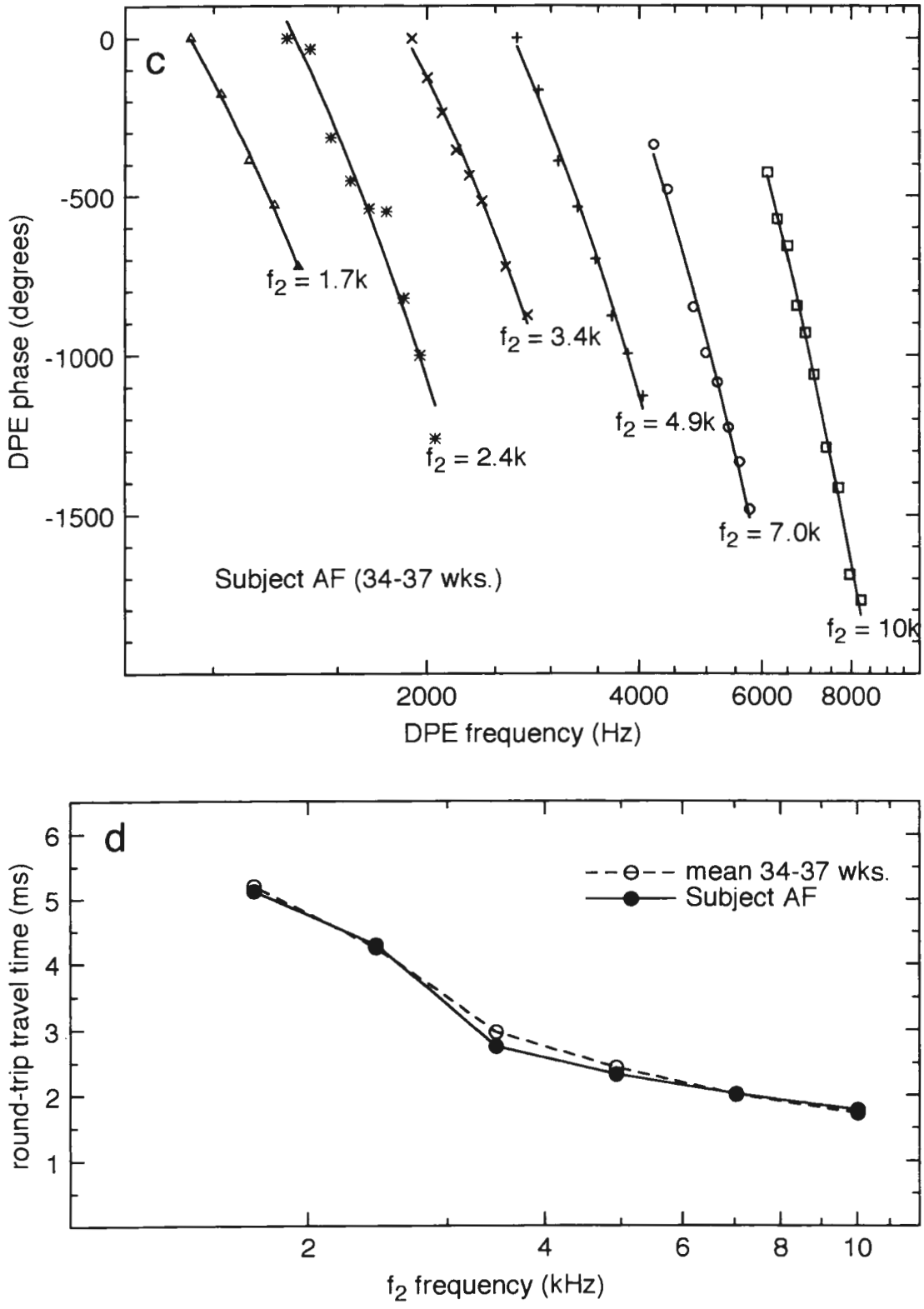

c
0
-500
-1000
-1500
DPE phase (degrees)
f_2 = 1.7k
f_2 = 2.4k
f_2 = 3.4k
f_2 = 4.9k
f_2 = 7.0k
f_2 = 10k
Subject AF (34-37 wks.)
2000
4000
6000
8000
DPE frequency (Hz)
d
6
5
4
3
2
1
round-trip travel time (ms)
mean 34-37 wks.
Subject AF
2
4
6
8
10
f_2 frequency (kHz)

Figure 3.9

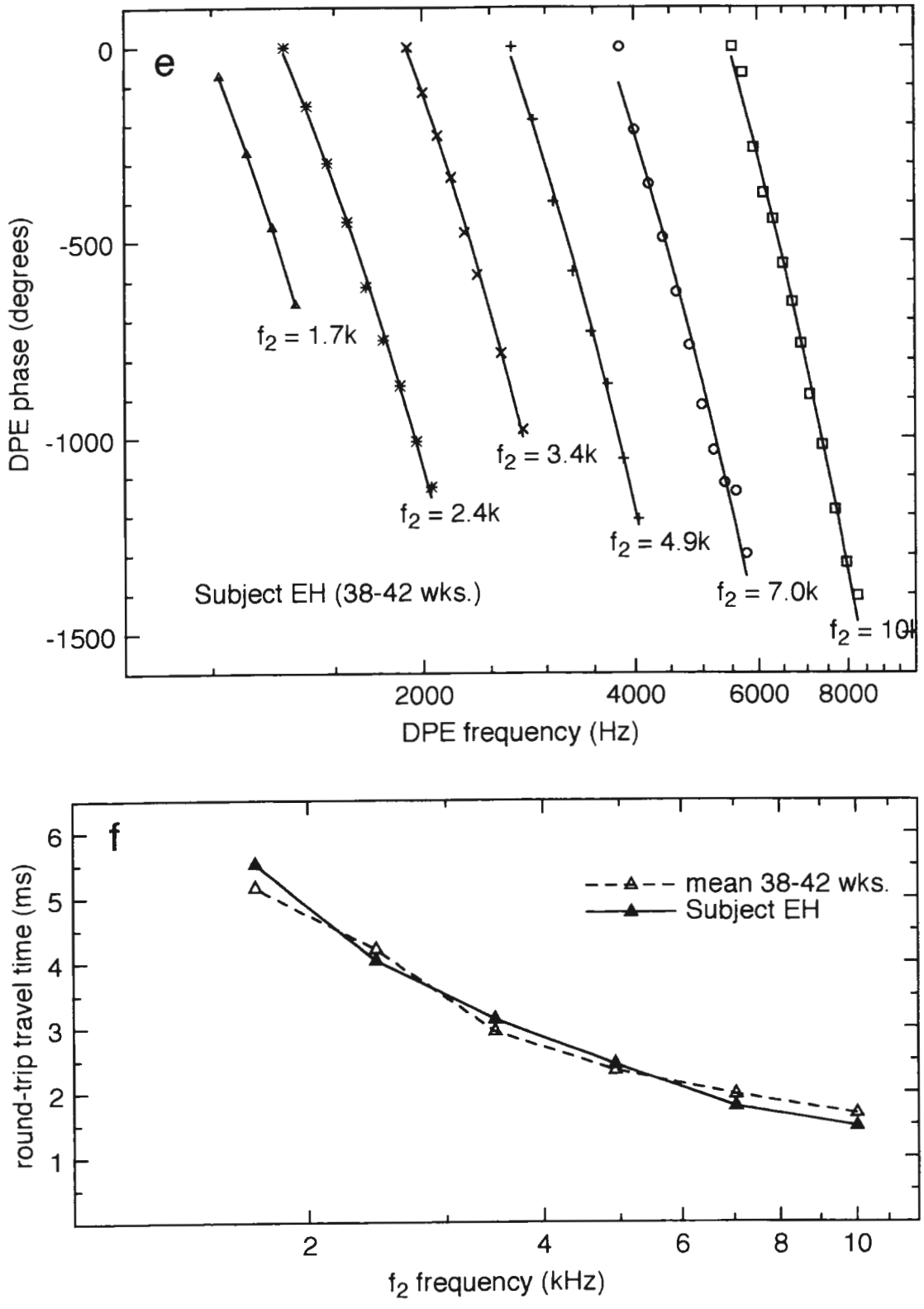
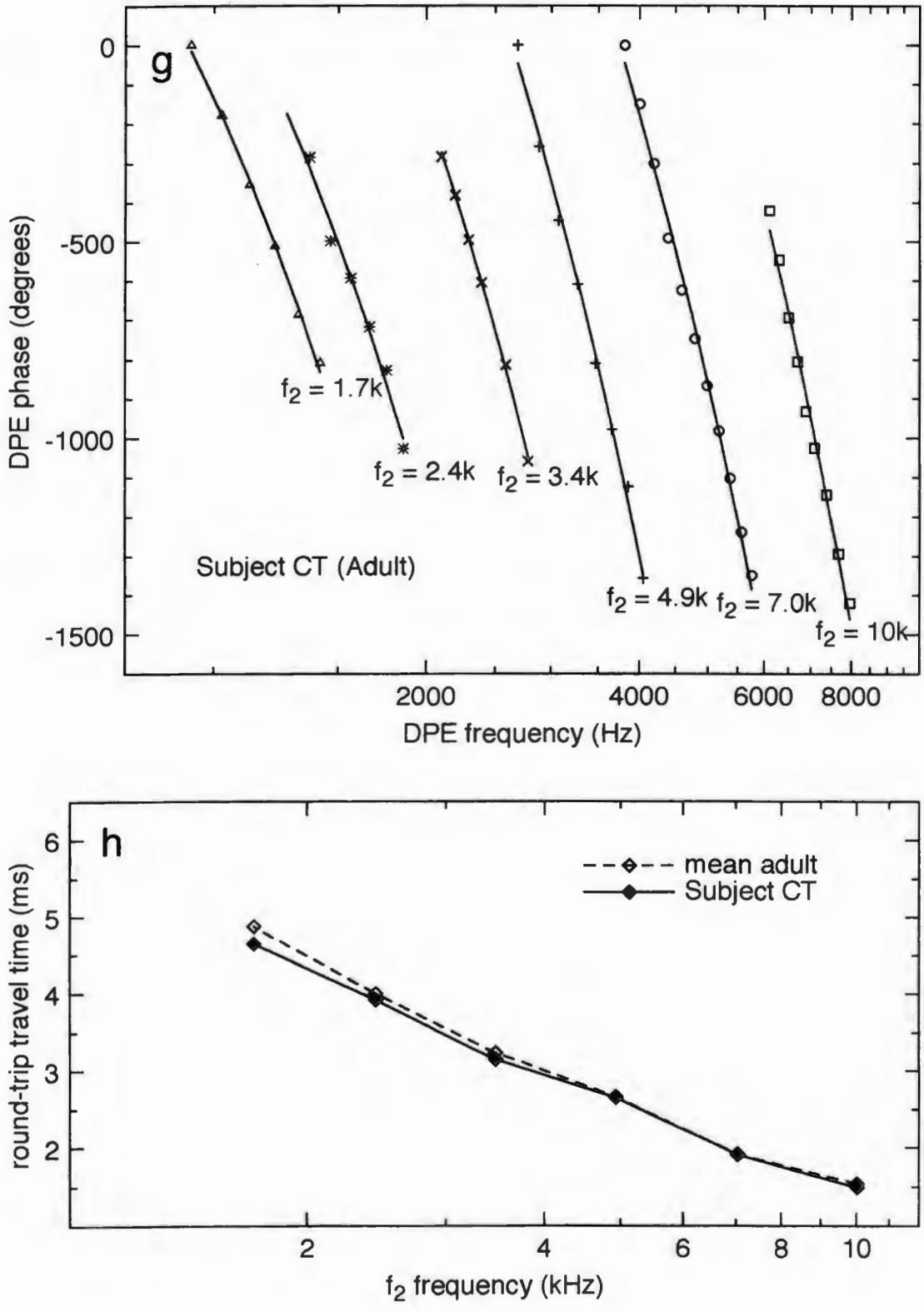

e
0
-500
-1000
-1500
DPE phase (degrees)
f_2 = 1.7k
f_2 = 2.4k
f_2 = 3.4k
f_2 = 4.9k
f_2 = 7.0k
f_2 = 10k
Subject EH (38-42 wks.)
2000
4000
6000
8000
DPE frequency (Hz)
f
6
5
4
3
2
1
round-trip travel time (ms)
mean 38-42 wks.
Subject EH
2
4
6
8
10
f_2 frequency (kHz)

Figure 3.9


g
0
-500
-1000
-1500
DPE phase (degrees)
f_2 = 1.7k
f_2 = 2.4k
f_2 = 3.4k
f_2 = 4.9k
f_2 = 7.0k
f_2 = 10k
Subject CT (Adult)
2000
4000
6000
8000
DPE frequency (Hz)
h
mean adult
Subject CT
round-trip travel time (ms)
2
3
4
5
6
2
4
6
8
10
f_2 frequency (kHz)

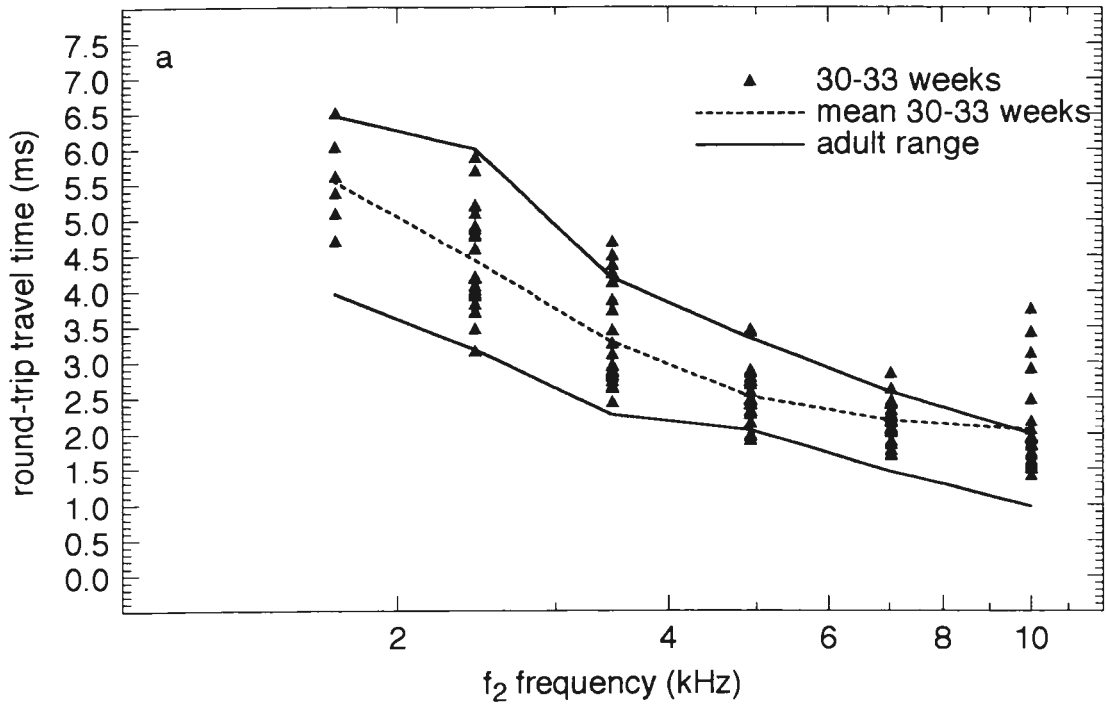
This same trend is shown for the age group data in Figure 3.10, which presents for each age group the individual data points, the curve through the mean values at each f_2 frequency and lines indicating the boundaries of the range of round-trip travel times for the adult group. A semi-logarithmic representation is used. Starting with Figure 3.10(a), one observes that a sizable fraction of the round-trip travel times for f_2 = 10 kHz are larger than found for the adult group, this number becomes smaller for the older newborn groups (Figures 3.10b,c). Figure 3.11 combines the curves connecting the group means at each f_2-frequency on a double logarithmic plot. One observes a tendency for the values in the youngest age group to be larger than for the other groups and in addition that the adult travel times tend to be larger than those for the newborns at 3.5 and 5 kHz. This becomes more obvious when the differences with the adult group are plotted (Figure 3.12). The 34-37 week olds and the 38-42 week olds appear to have the same difference function, whereas the differences for the youngest age group have roughly the same shape across intensity but are slightly larger. Significant differences (details in Appendix A) at the $p < 0.01$ level are indicated with a solid symbol. Detailed group by group comparisons are presented in Table III.2. At both high and low f_2 frequencies the difference was positive and was indicative of a larger travel time in the newborns, however, for the mid-frequencies the negative difference suggested a shorter travel time for the newborns.

Age and Frequency Dependence of the Optimum f_2/f_1 Ratio

The optimum f_2/f_1 ratio is defined as the ratio between the two primaries (f_2 and f_1) which results in the largest $2f_1$-f_2 (DPE) emission amplitude. For a fixed f_2 frequency and by changing f_1 from a ratio of 1.3 to 1.1, the largest DPE amplitude is usually found at some intermediate value. The optimum f_2/f_1 ratios are indicated by the ▼s and the numerical values are shown in Figure 3.13, but only for those values where the DPE amplitude exceeds the noise floor by 5 dB. Each of the six f_2 frequencies has its own

Figure 3.10 The raw data and group mean round-trip travel times are plotted for each group with the range of adult values. Panel (a) depicts the 30-33 weeks preterm group, (b) the 34-37 weeks preterm group, (c) the 38-42 weeks term group and (d) the adult group.

Figure 3.10


a
30-33 weeks
mean 30-33 weeks
adult range
round-trip travel time (ms)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2
4
6
8
10
f2 frequency (kHz)

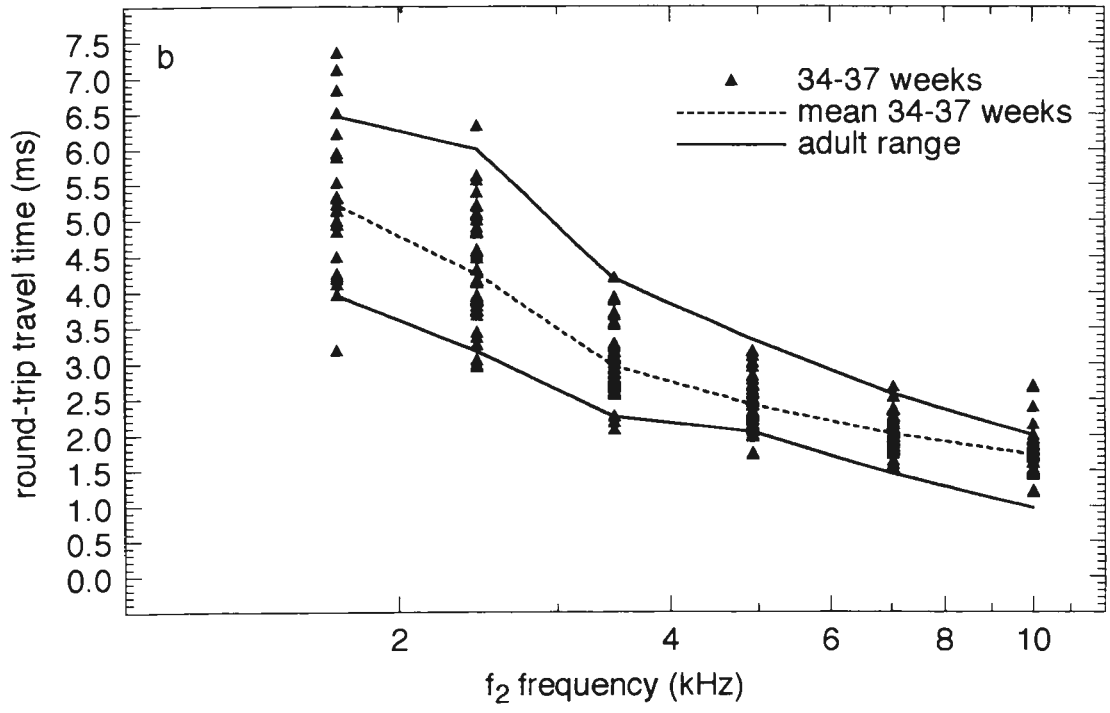
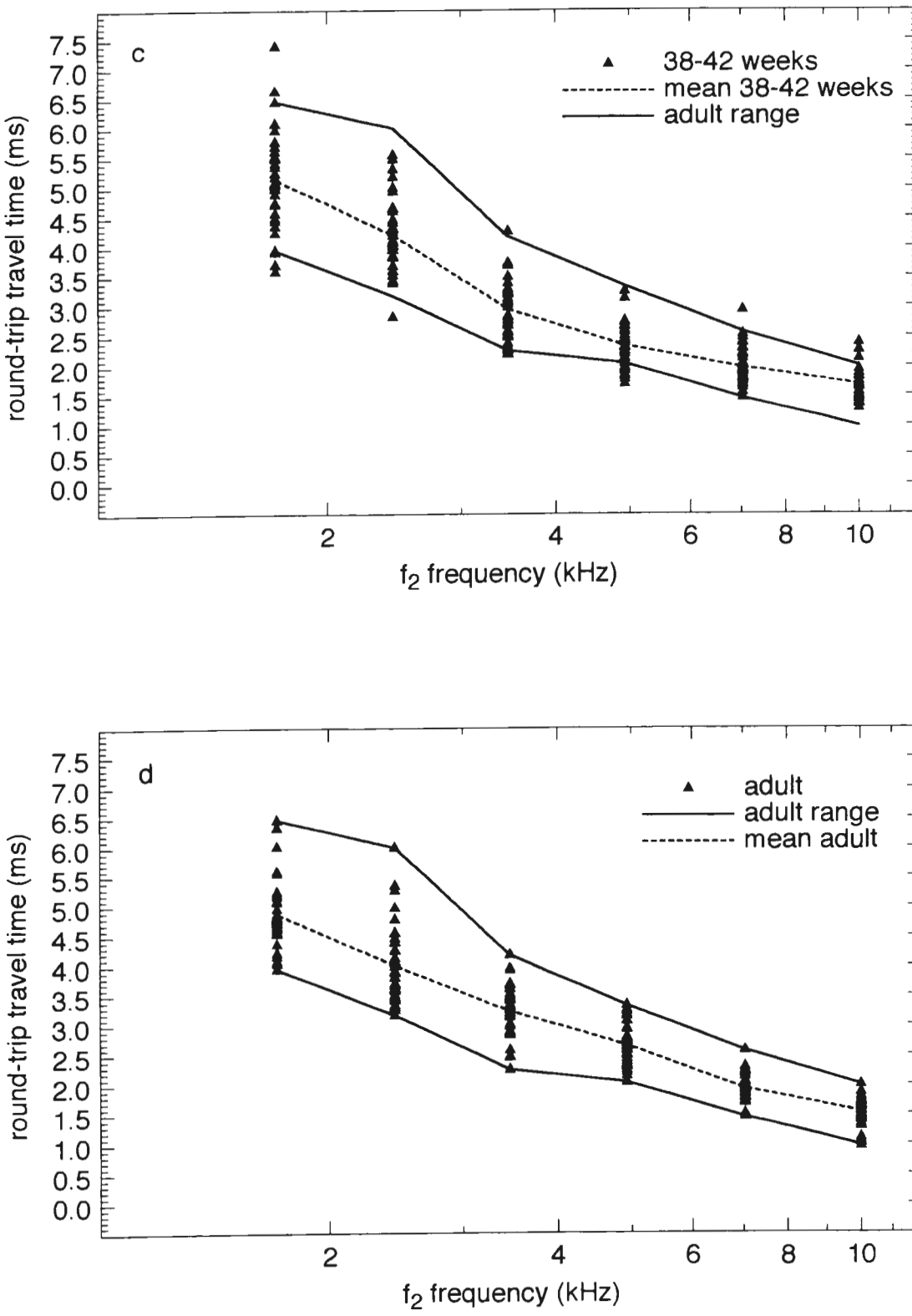

b
34-37 weeks
mean 34-37 weeks
adult range
round-trip travel time (ms)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2
4
6
8
10
f2 frequency (kHz)

Figure 3.10


c
38-42 weeks
mean 38-42 weeks
adult range
round-trip travel time (ms)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2
4
6
8
10
f2 frequency (kHz)
d
adult
adult range
mean adult
round-trip travel time (ms)
f2 frequency (kHz)

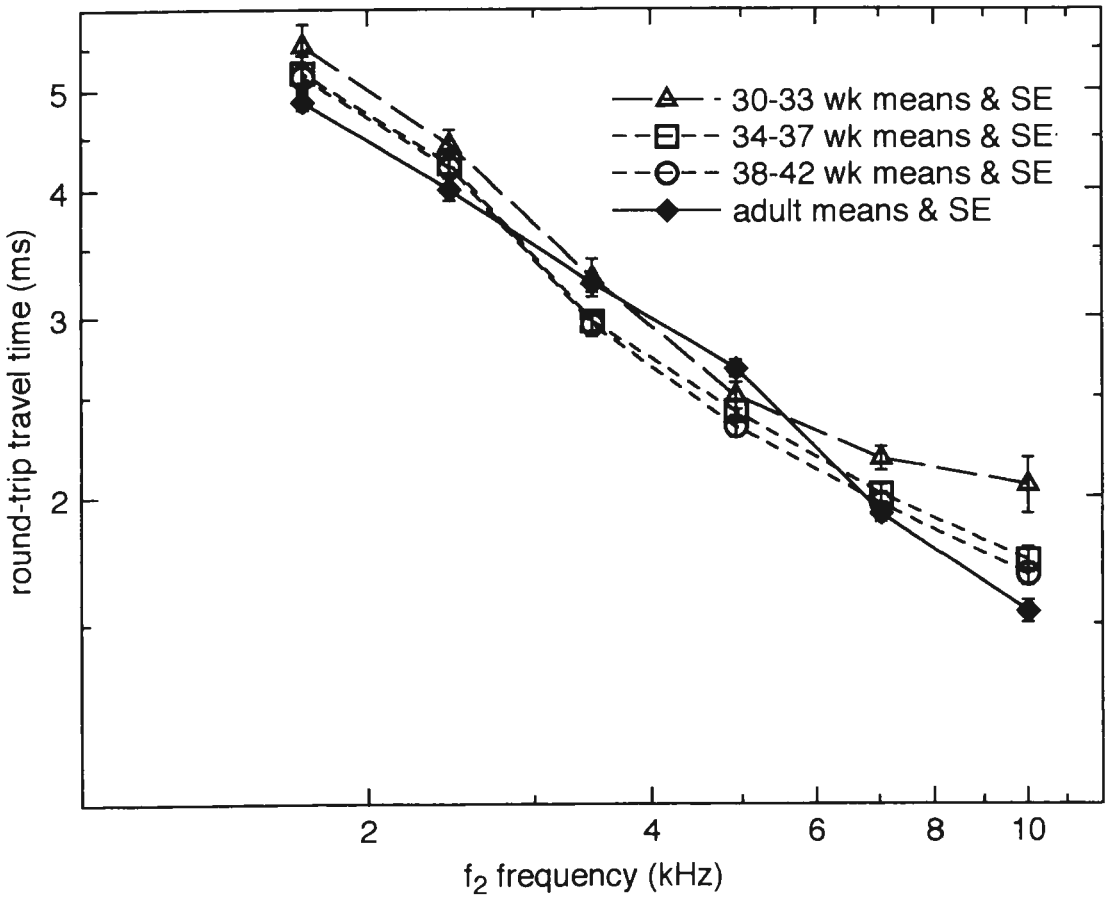


Figure 3.11 The mean round-trip travel times for each of the four groups.

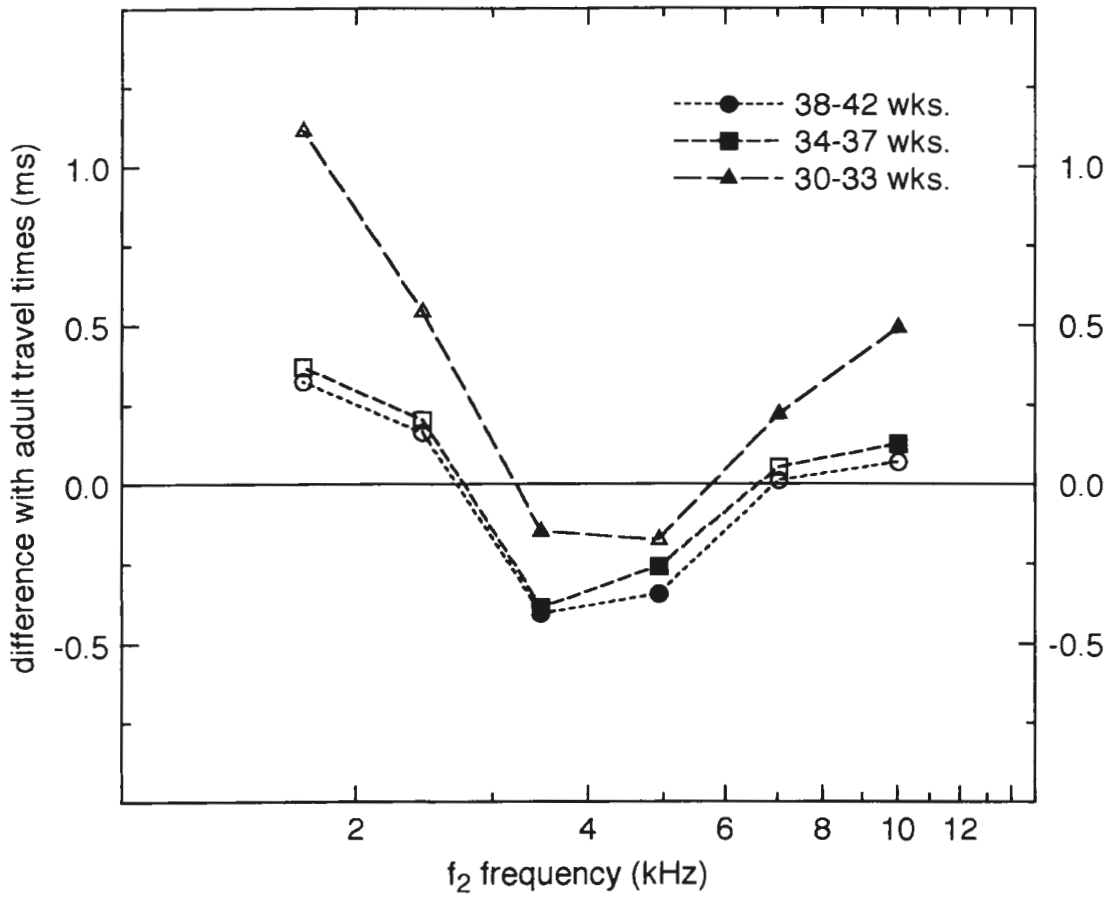


Figure 3.12 The mean adult travel times subtracted from the mean round-trip times of the three newborn groups. The difference is plotted for each f_2 frequency. The solid symbols indicates values which are significantly different ($p<0.01$) from the Adult group.

Significant difference by frequency for each group (unpaired)

f_2 frequency (kHz)	Group	34-37 wks.	38-42 wks.	Adults
10.0098	30-33 wks.	.009**	.001***	.001***
	34-37 wks.		.396	.004***
	38-42 wks.			.018*
7.0313	30-33 wks.	.018*	.007**	.001***
	34-37 wks.		.504	.108
	38-42 wks.			.441
4.9316	30-33 wks.	.348	.071	.079
	34-37 wks.		.277	.002***
	38-42 wks.			.001***
3.4668	30-33 wks.	.036*	.028*	.001***
	34-37 wks.		.837	.001***
	38-42 wks.			.004***
2.4414	30-33 wks.	.358	.184	.016*
	34-37 wks.		.801	.134
	38-42 wks.			.142
1.7090	30-33 wks.	.462	.294	.017*
	34-37 wks.		.849	.110
	38-42 wks.			.093

(* $p < 0.05$)
(** $p < 0.01$)
(*** $p < 0.005$)

Table III.2 Differences in round-trip travel time between groups for each frequency.

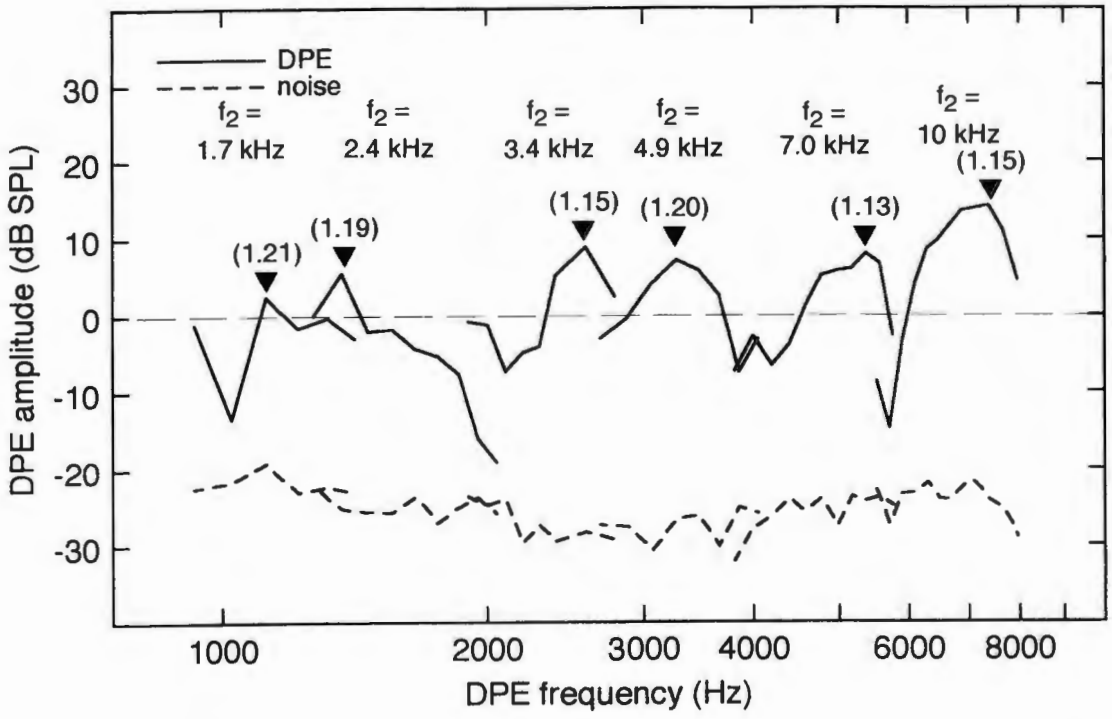


Figure 3.13 An example of the DPEs generated by holding f_2 constant and sweeping f_1 from a ratio of 1.3 to 1.1 for six different f_2 frequencies. Note the ▼ which indicates the largest amplitude emission for the f_1-sweep at each f_2 frequency. The optimum f_2/f_1 ratio is that combination of f_2 and f_1 primaries which generates the largest amplitude emission and is noted in the parenthesis above the ▼.

optimum ratio. Examples for subjects from each age group are shown in Figure 3.14; one notices the tendency of the optimum ratios to become smaller for increasing f_2 frequency but with limited effect of age.

For each age group all DPE amplitude-frequency plots were combined in Figure 3.15. and the average optimum f_1 frequency for the particular f_2 frequency (the optimum f_2/f_1 ratio) is indicated by the vertical dashed line. From the distribution of curves around this dashed line one already notices that the optimum f_1 was relatively lower for lower f_2 (this means a higher f_2/f_1 ratio) and relatively higher for higher f_2 (thus a lower f_2/f_1 ratio). Not too much of an age effect was apparent. Table III.3 gives the mean optimum ratios for each age group and frequency. A repeated measures ANOVA (one within, one between) indicated that there was no main effect of age but that there was a main effect of frequency ($p < 0.0001$). Figure 3.16 shows the mean optimum ratios, collapsed across all age groups, as a function of f_2 frequency. It appears that for frequencies below 4 kHz, to take a value in between 3.5 and 4.9 kHz, the optimum ratio was high, about 1.22, and above 4 kHz the optimum ratio was lower and around 1.18. Table III.4 summarizes the pairwise comparisons between frequencies; there were no differences between the optimum ratios for $f_2 < 4$ kHz and no difference between the optimum ratios for $f_2 > 4$ kHz, however, all frequencies in the low f_2 group showed significantly higher optimum ratios than all frequencies in the high f_2 group.

Intensity Dependence of the Optimum f_2/f_1 Ratio in Adults

An adult group was used to study intensity effects on the optimum f_2/f_1 ratio at six different intensity levels. Examples from one subject illustrating this were already shown in Figure 3.1. The lowest two intensity levels were left out of the analysis due to the low percentage of emissions. Data were combined for f_2 intensities of 25 and 30 dB, for 35 and 40 dB and for 45 and 50 dB SPL. This grouping was suggested from the pair wise

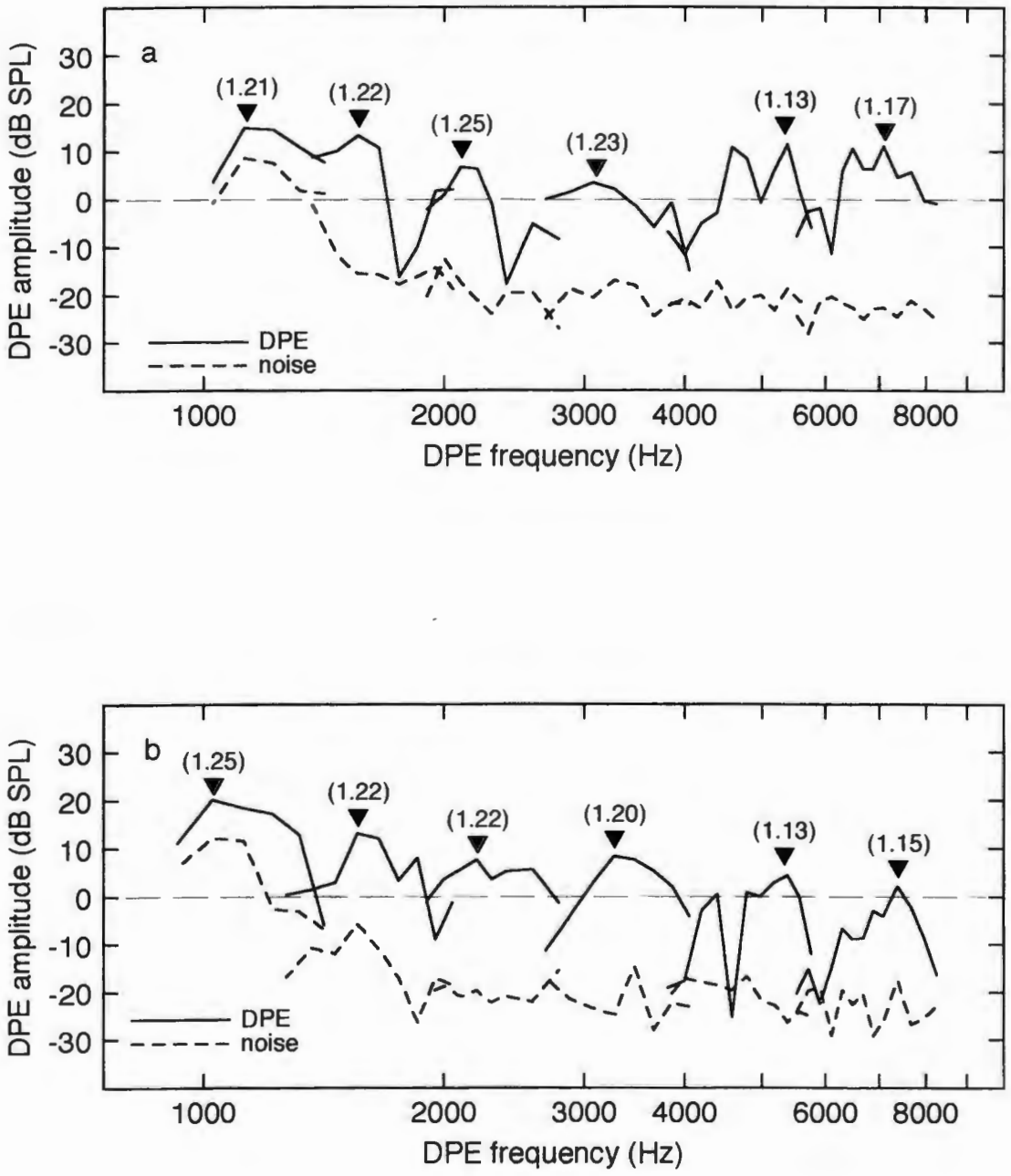


Figure 3.14 Examples of the DPEs from each of the four groups: (a) 30-33 wks.; (b) 34-37 wks.; (c) 38-42 wks.; and, (d) Adult. The ▼ indicates the largest emission for that f_2 frequency and the optimum ratio which corresponds to that particular f_2 frequency is noted in the parenthesis above the ▼.

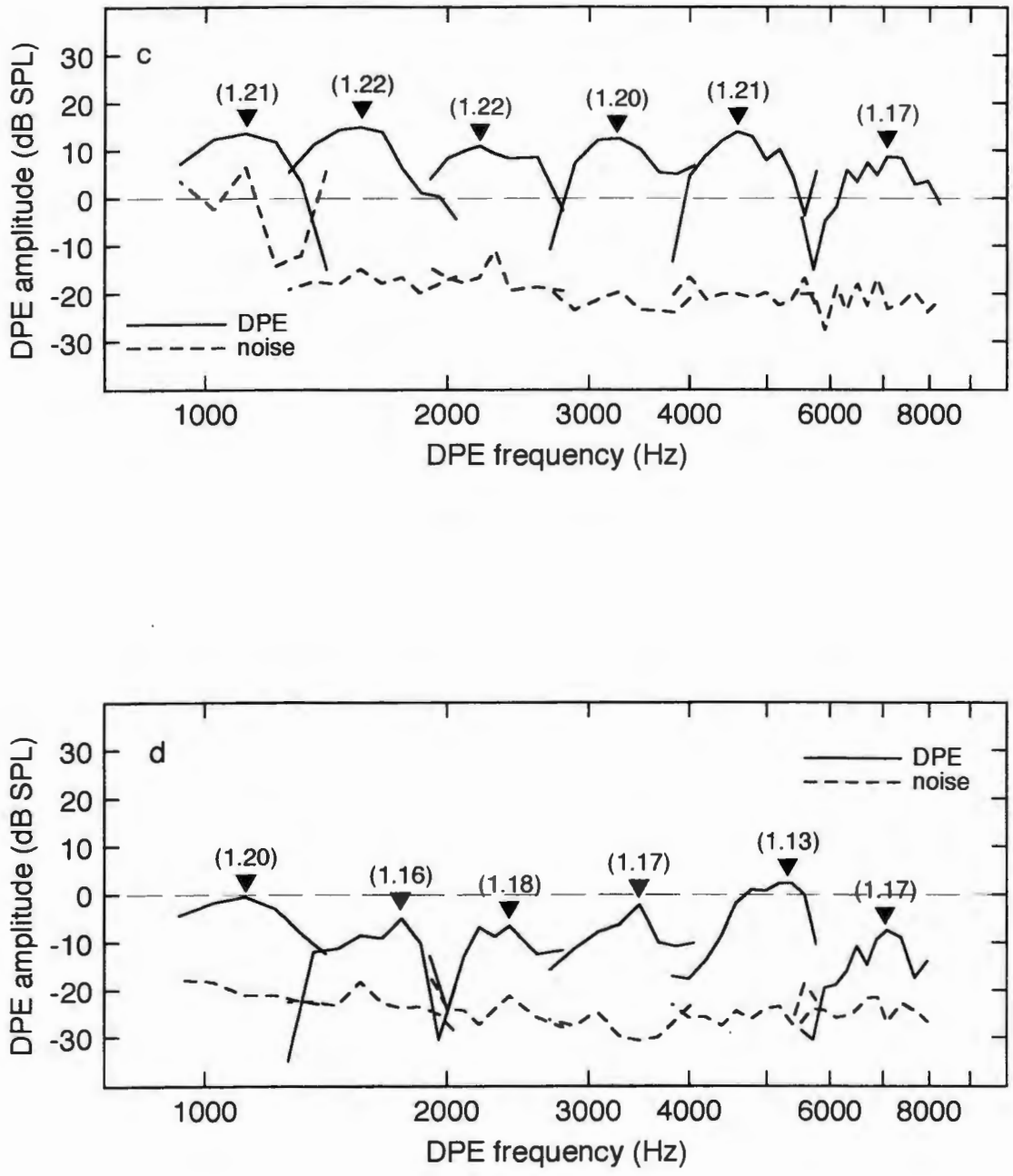


Figure 3.14 Examples of the DPEs from each of the four groups: (a) 30-33 wks.; (b) 34-37 wks; (c) 38-42 wks; and, (d) Adult. The ▼ indicates the largest emission for that f_2 frequency and the optimum ratio which corresponds to that particular f_2 frequency is noted in the parenthesis above the ▼.

Figure 3.15 Mean f_2/f_1 ratio for each f_2 frequency. Each group shows a frequency dependent ratio when compared to the optimum ratio. The ratios for the lower f_2 frequencies have a higher ratio than those of the higher f_2 frequency. Panel (a) is the 30-33 weeks (Preterm) group, (b) is the 34-37 weeks Preterm group, (c) is the 38-42 weeks group and (d) is from the Adult group.

Figure 3.15

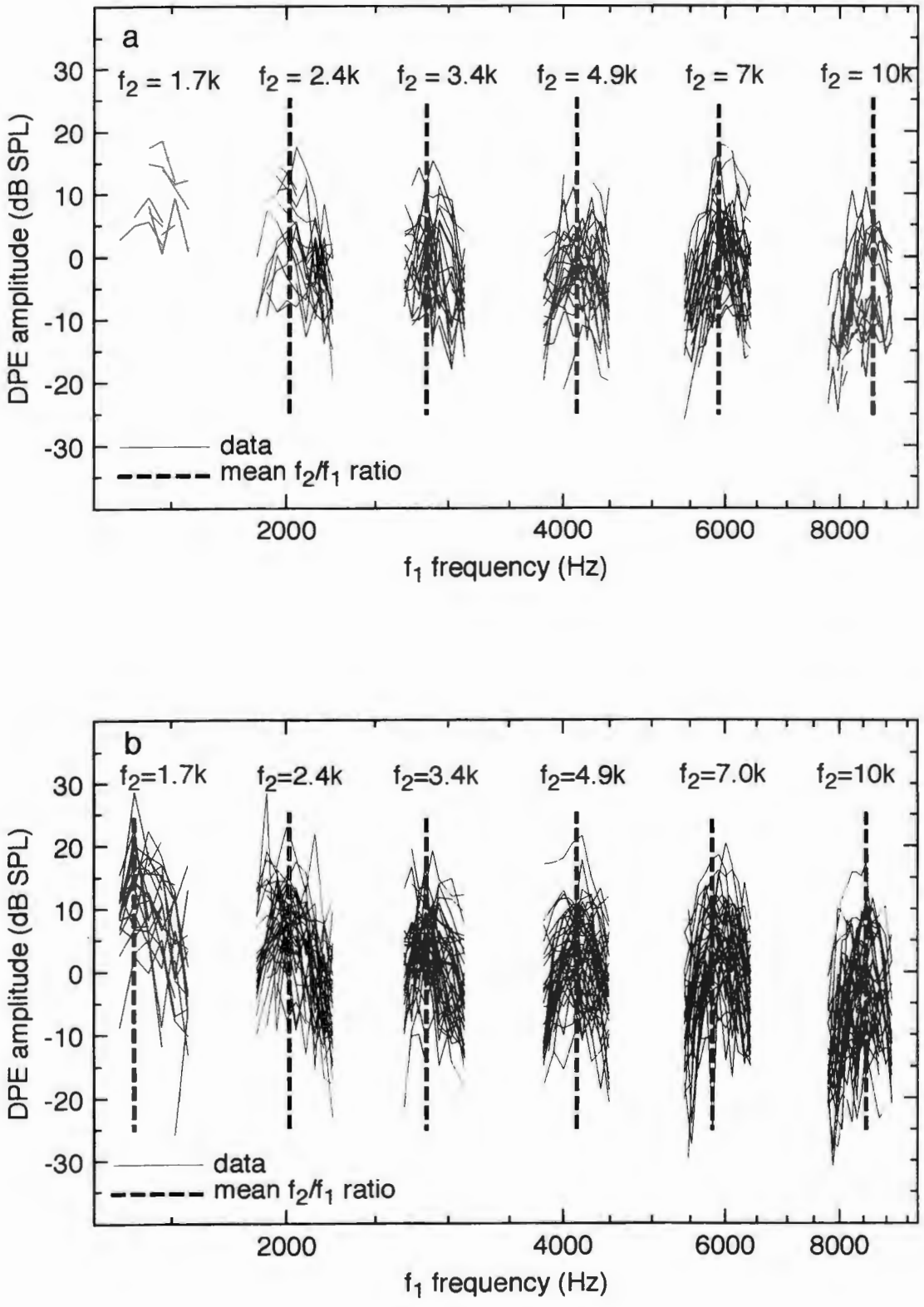
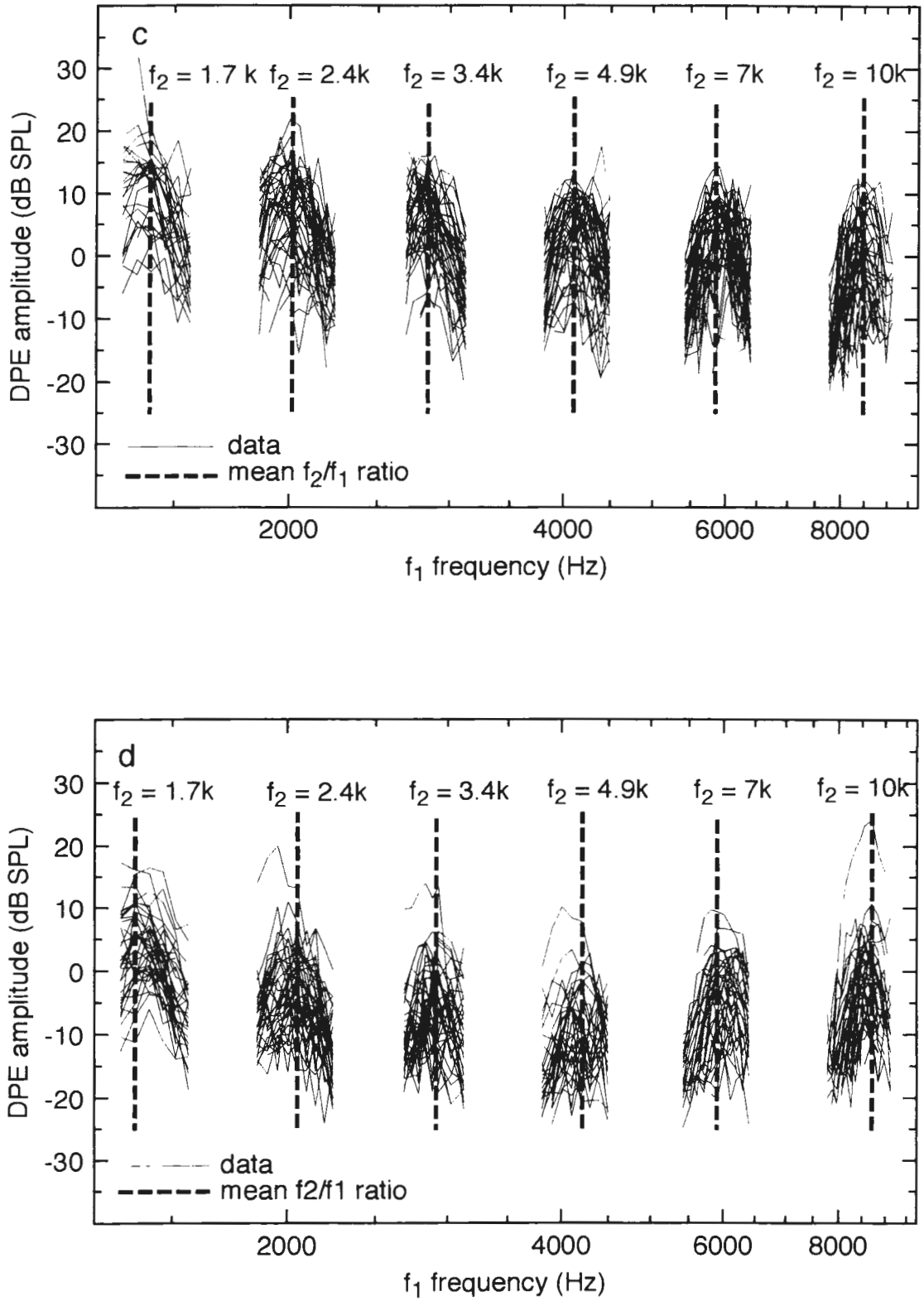

a
f_2 = 1.7k
f_2 = 2.4k
f_2 = 3.4k
f_2 = 4.9k
f_2 = 7k
f_2 = 10k
DPE amplitude (dB SPL)
30
20
10
0
-10
-20
-30
data
mean f_2/f_1 ratio
2000
4000
6000
8000
f_1 frequency (Hz)
b
f_2=1.7k
f_2=2.4k
f_2=3.4k
f_2=4.9k
f_2=7.0k
f_2=10k
DPE amplitude (dB SPL)
30
20
10
0
-10
-20
-30
data
mean f_2/f_1 ratio
2000
4000
6000
8000
f_1 frequency (Hz)

Figure 3.15


c
f_2 = 1.7 k
f_2 = 2.4k
f_2 = 3.4k
f_2 = 4.9k
f_2 = 7k
f_2 = 10k
DPE amplitude (dB SPL)
30
20
10
0
-10
-20
-30
data
mean f_2/f_1 ratio
2000
4000
6000
8000
f_1 frequency (Hz)
d
f_2 = 1.7k
f_2 = 2.4k
f_2 = 3.4k
f_2 = 4.9k
f_2 = 7k
f_2 = 10k
DPE amplitude (dB SPL)
30
20
10
0
-10
-20
-30
data
mean f2/f1 ratio
2000
4000
6000
8000
f_1 frequency (Hz)

f_2 frequency (Hz)	30-33 wks.	34-37 wks.	38-42 wks.	adult
10009.8	1.174	1.175	1.186	1.164
7031.3	1.170	1.188	1.187	1.174
4931.6	1.186	1.184	1.183	1.177
3466.8	1.216	1.223	1.240	1.197
2441.4	1.202	1.221	1.224	1.212
1709.0	*	1.232	1.224	1.230

* Insufficient data points

Table III.3 Mean optimum f_2/f_1 ratios for each group. Note that the Preterm (30-33 wks.) group had insufficient values at 1.7 kHz (f_2 frequency) to calculate the mean ratio.

Paired t-test
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value
f2 = 10, f2 = 7	-4.990E-3	140	-1.351	.1789
f2 = 10, f2 = 4	-6.634E-3	142	-1.635	.1043
f2 = 10, f2 = 3	-.044	139	-13.215	<.0001
f2 = 10, f2 = 2	-.042	140	-10.655	<.0001
f2 = 10, f2 = 1	-.051	112	-9.919	<.0001
f2 = 7, f2 = 4	-1.088E-3	140	-.268	.7887
f2 = 7, f2 = 3	-.038	137	-10.401	<.0001
f2 = 7, f2 = 2	-.035	137	-8.232	<.0001
f2 = 7, f2 = 1	-.041	109	-8.363	<.0001
f2 = 4, f2 = 3	-.038	139	-10.029	<.0001
f2 = 4, f2 = 2	-.035	139	-8.298	<.0001
f2 = 4, f2 = 1	-.045	111	-8.959	<.0001
f2 = 3, f2 = 2	1.549E-3	138	.436	.6635
f2 = 3, f2 = 1	-8.791E-3	111	-1.764	.0805
f2 = 2, f2 = 1	-9.952E-3	112	-1.848	.0673

Table III.4 Differences between f_2 frequencies for the optimum f_2/f_1 ratio across all groups.

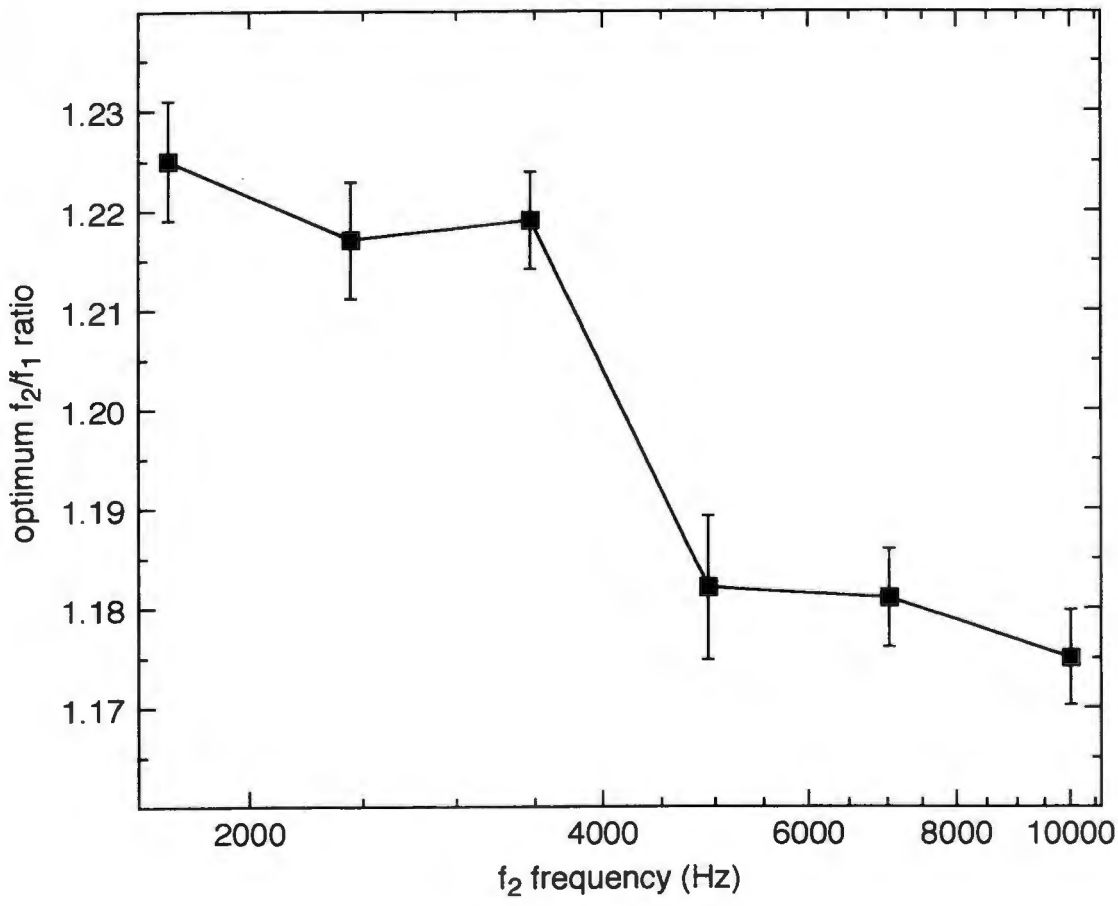


Figure 3.16 Optimum f_2/f_1 ratios as a function of f_2 frequency across all four age groups. Standard errors are indicated by error bars for each frequency.

similarity of the exponents of the power function curve fits shown in Figure 3.6.

Mean optimum ratios for the three intensity groups are shown in Figure 3.17. The results suggested a trend for lower optimum ratios for lower f_2 intensities, except at 3.5 kHz where there was hardly any difference between the three intensity groups. Another representation, with optimum ratio plotted against intensity for each of the six f_2 frequencies is shown in Figure 3.18. Regression analysis showed that the slopes of these lines were significantly different from zero at all frequencies except f_2 = 3.4 kHz and 7.0 kHz (Appendix C).

Age Dependence of DPE Amplitude

For this study the DPE amplitude was measured at two different intensity levels while the stimuli were swept across frequency for a fixed f_2/f_1 ratio of 1.2. As our previous analysis showed this was in between the low and high ratios found for high and low f_2 frequencies. The intensity of f_1 was kept at 65 dB SPL and that of f_2 was either 55 dB or 50 dB SPL. Emissions were obtained at 12 frequencies, two per octave, and an example from each age group is shown in Figure 3.19.

Mean DPE amplitudes and corresponding noise floors are plotted in Figure 3.20 together with the standard errors of the mean. The lowest three frequencies contained an insufficient number of emission data that were 5 dB above the noise floor, so these three frequencies were omitted from further analysis. There was little difference for DPE amplitude for f_2 = 50 dB or f_2 = 55 dB SPL as shown in Table III.5. Appendix B shows results from grouped t-tests which show that there is no significant difference between the two intensity levels at any of the nine frequencies.

Thus the data were collapsed across f_2 intensities and the mean data as a function of f_2 frequency are shown in Figure 3.21. It is clear that, except for the youngest age group at 10 kHz, the adult DPE amplitudes were much lower than those of the newborns. A

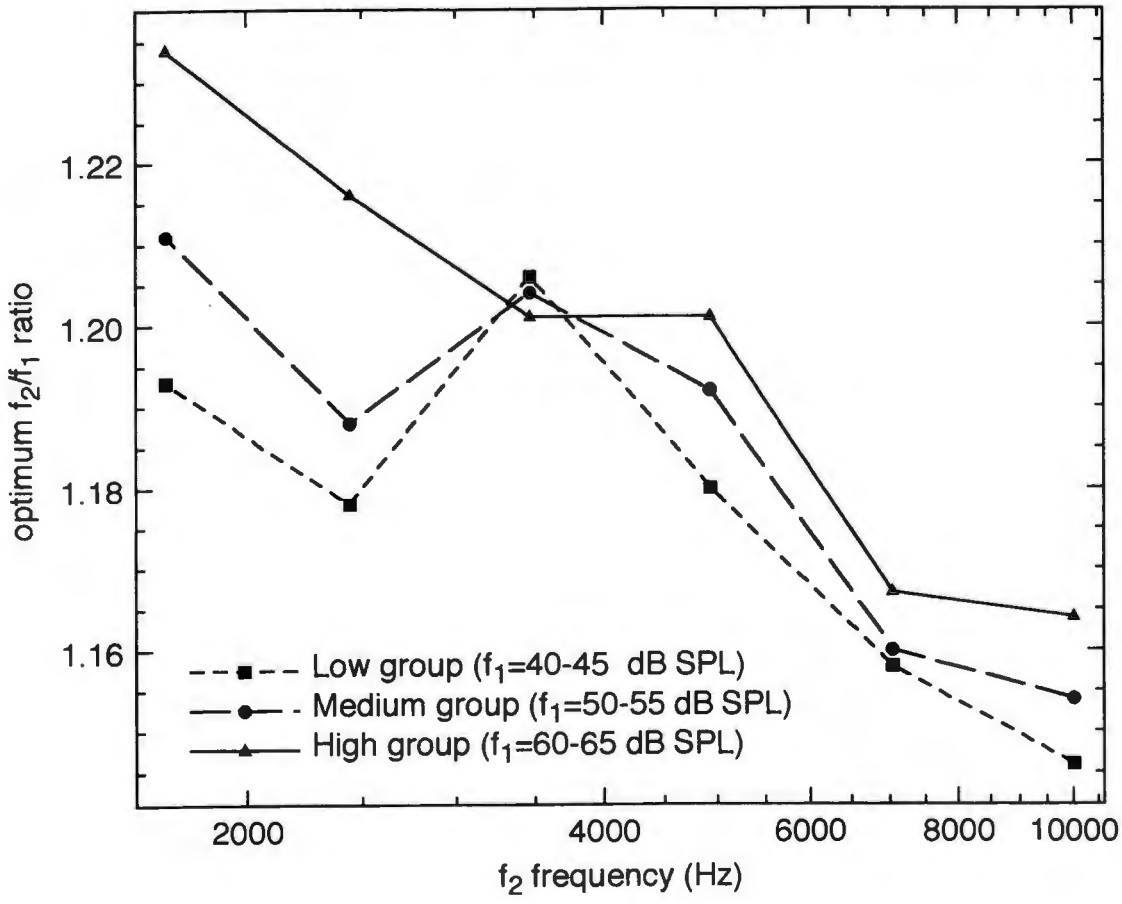


Figure 3.17 Mean optimum f_2/f_1 ratios for the three groups of stimulus intensities.

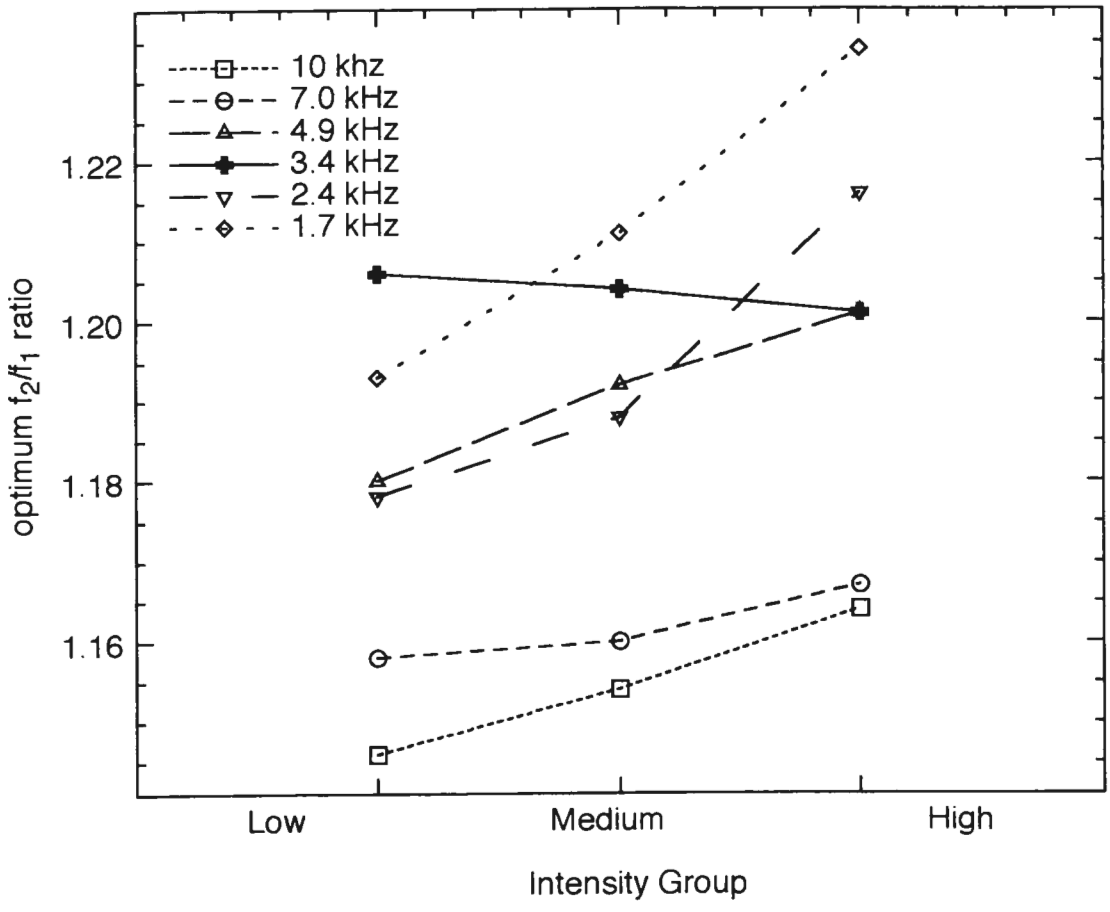


Figure 3.18 Optimum $f_2 \backslash f_1$ ratio at each of the six f_2 frequencies grouped according to the three intensity groups.

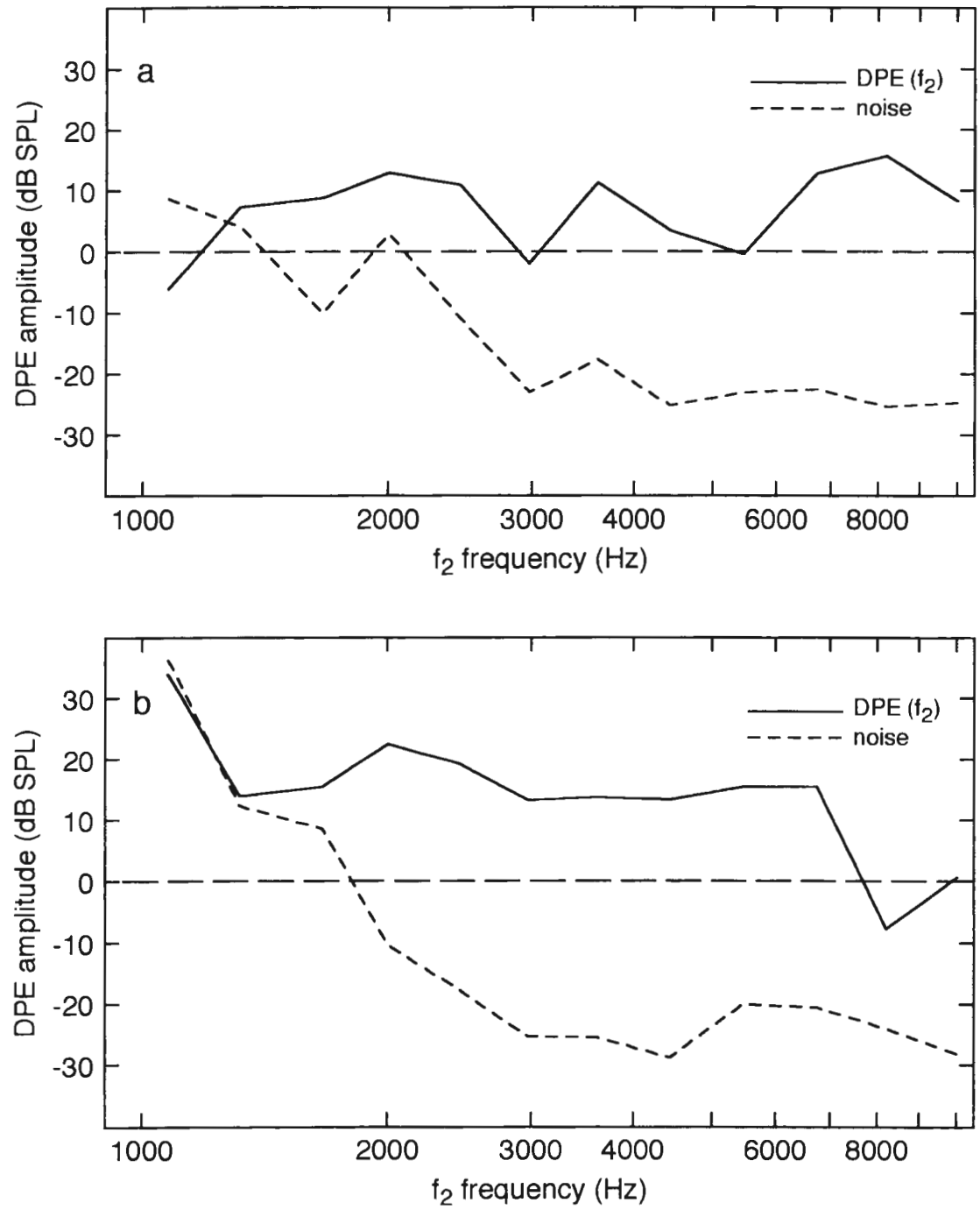


Figure 3.19 Examples of emissions from a subject in each group. Panel (a) is Subject SC from Group 1 (30-33 wks.), Panel (b) is Subject AF from Group 2 (34-37 wks.), Panel (c) is Subject SB from Group 3 (38-42 wks.) and Panel (d) is Subject CT from Group 4 (Adult). The solid line is the DPE amplitude and the dashed line is the noise floor.

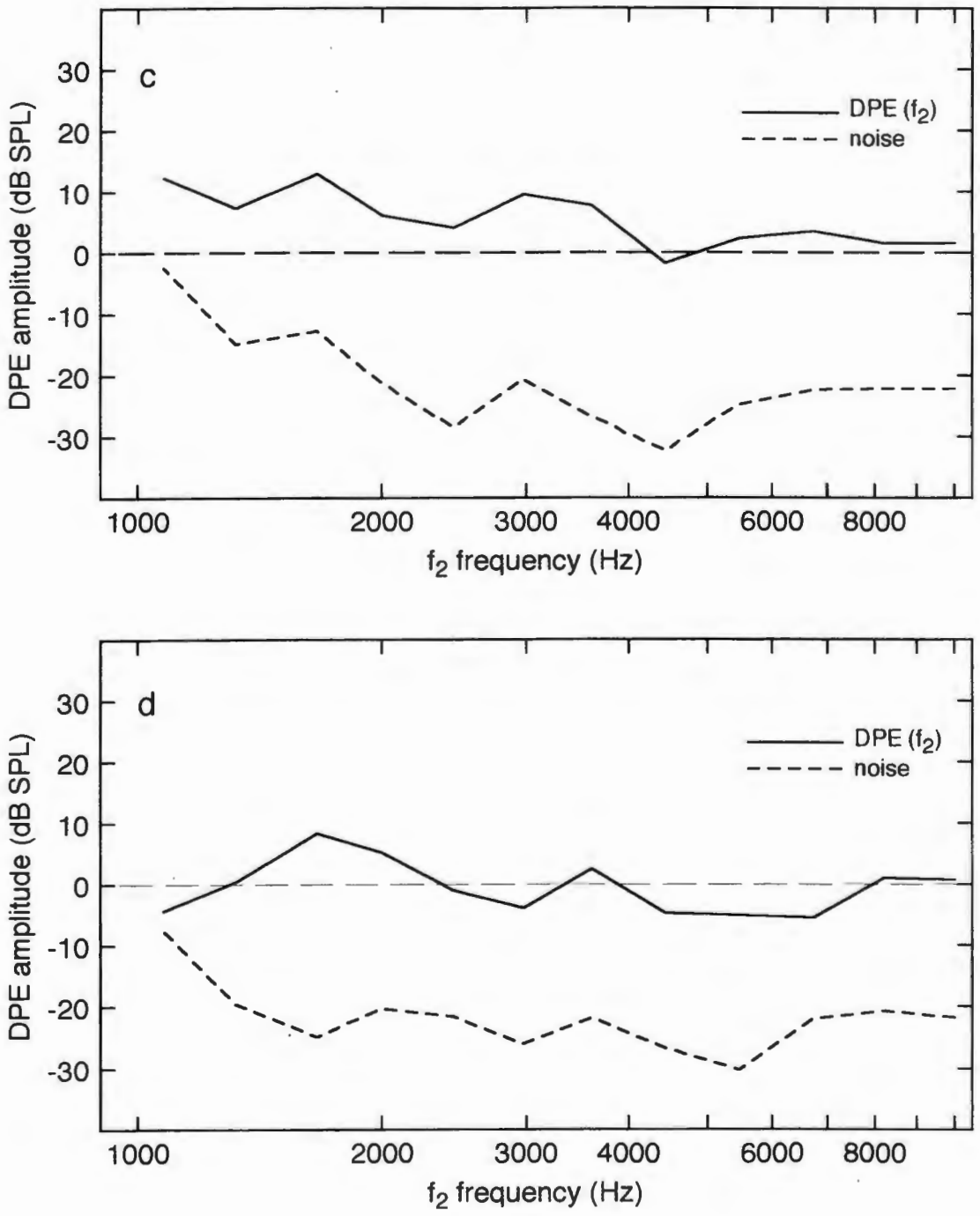


Figure 3.19 Examples of emissions from a subject in each group. Panel (a) is Subject SC from Group 1 (30-33 wks.), Panel (b) is Subject AF from Group 2 (34-37 wks.), Panel (c) is Subject SB from Group 3 (38-42 wks.) and Panel (d) is Subject CT from Group 4 (Adult). The solid line is the DPE amplitude and the dashed line is the noise floor.

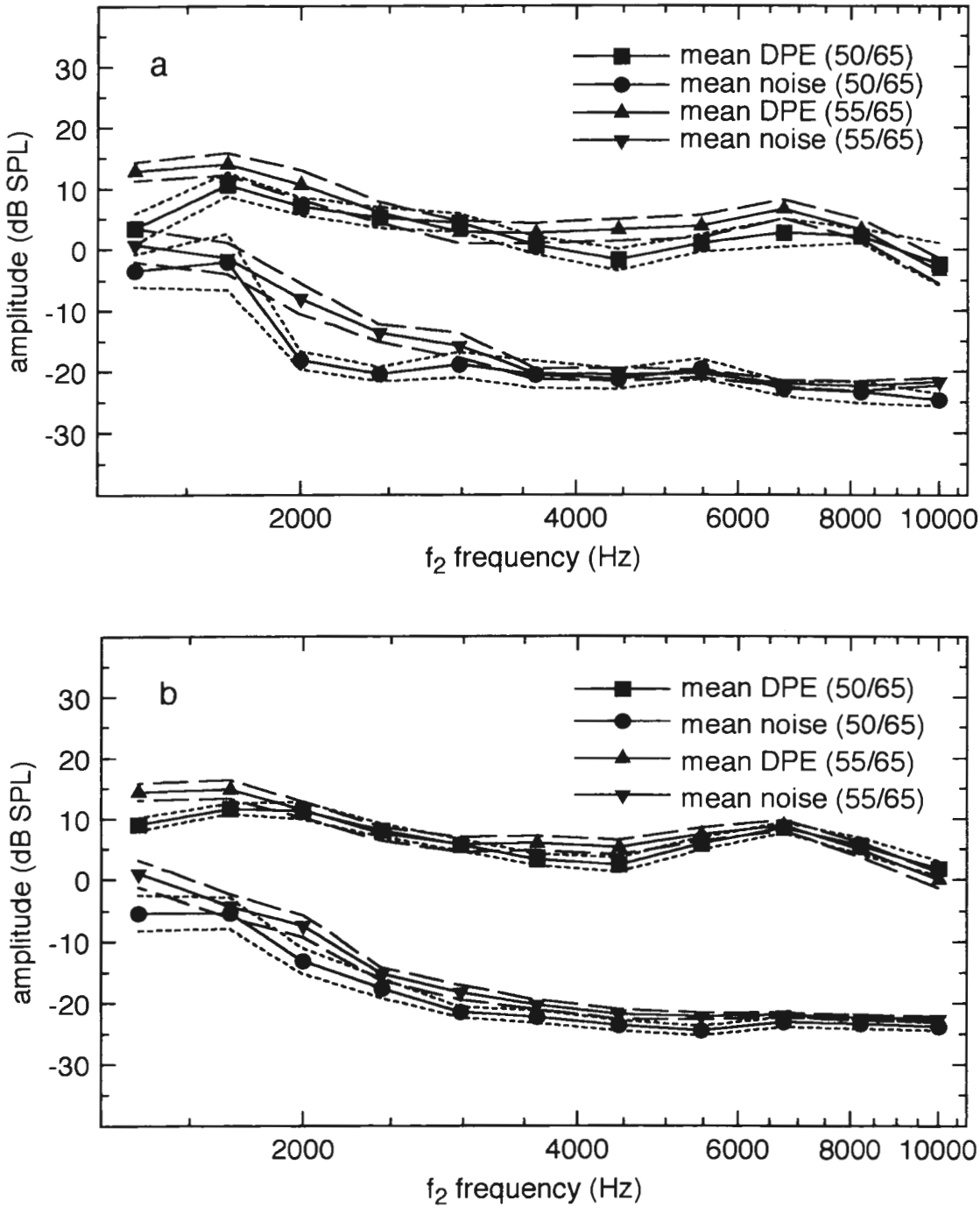


Figure 3.20 Mean DPE amplitude results for L1-L2 = 10 and 15 dB and their corresponding noise floors. (a) the 30-33 wks. group, (b) the 34-37 wks. group, (c) the 38-42 wks. group, and (d) the adult group. Dashed lines indicate standard error of the mean.

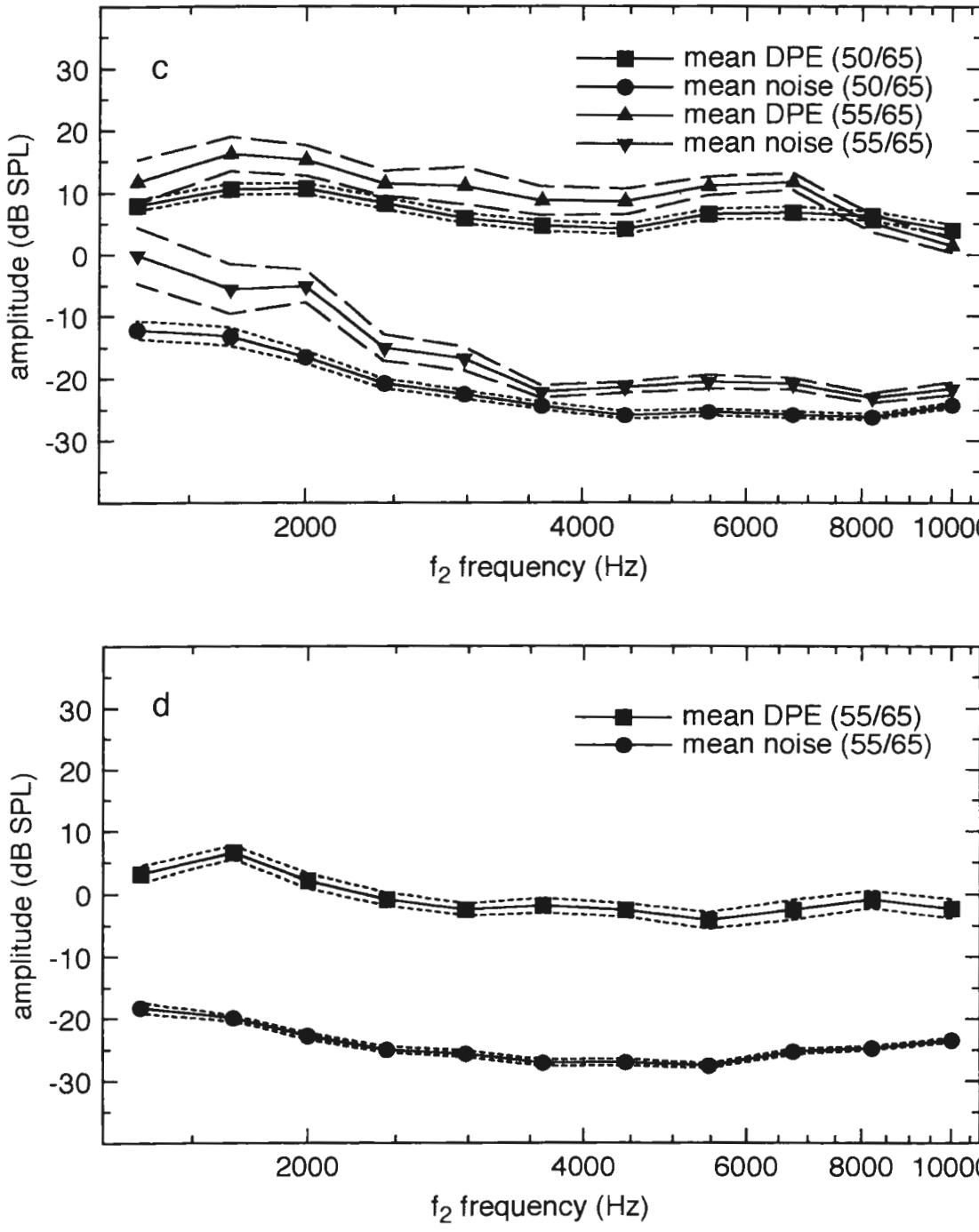


Figure 3.20 Mean DPE amplitude results for L1-L2 = 10 and 15 dB and their corresponding noise floors. (a) the 30-33 wks. group, (b) the 34-37 wks. group, (c) the 38-42 wks. group, and (d) the adult group. Dashed lines indicate standard error of the mean.

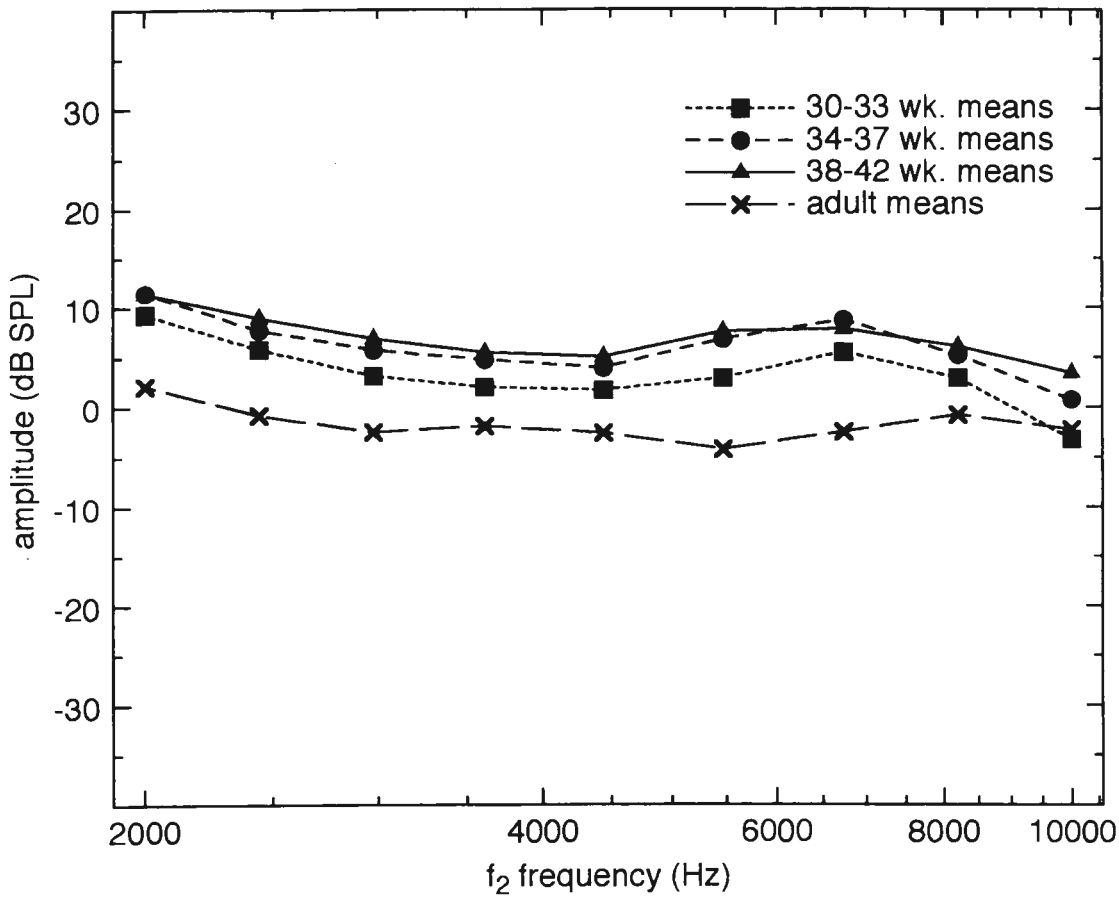


Figure 3.21 Mean DPE amplitude results for all four groups. Note that the adult group has a lower amplitude than all other groups.

f_2 frequency (Hz)	Preterm Group (1) 30-33 wks.	Preterm Group (2) 34-37 wks.	Term Group (3) 38-42 wks.
10009.8	.8216	.3376	.1776
8203.13	.7144	.7436	.4897
6738.28	.1932	.8009	.0188
5468.75	.3800	.2970	.0176
4443.36	.1321	.1011	.0272
3613.28	.4985	.0960	.0610
2978.52	.6175	.9471	.0256
2441.41	.7950	.7244	.1357
2001.95	.3332	.9245	.0558

Table III.5 Differences between stimulus levels L1-L2 = 10 dB and L1-L2 = 15 dB for each of the preterm and term groups. ($p<0.01$)

significant interaction was found between age and frequency ($p < 0.0001$). A post hoc analysis was carried out using the Bonferroni-Dunn adjustment and the results are summarized in Table III.6. Two different frequencies showed significant differences in DPE amplitude between the early preterm (30-33 wks.) and the term (38-42 wks.) groups. There were no significant differences between the 34-37 week olds and the term group and the 30-33 week olds and the 34-37 week olds. The differences between the newborns and the adults became more visible when the differences were plotted (Figure 3.22). At all frequencies except 10 kHz, the two oldest newborn groups were significantly different from the adult group, and the youngest newborn group was significantly different at most frequencies except 3.6, 4.4, 8.2 and 10 kHz.

Significant difference by frequency for each group

f_2 frequency (Hz)	Group	34-37 wks.	38-42 wks.	Adults
10009	30-33 wks.	.0325	.0005*	.6256
	34-37 wks.		.0817	.0617
	38-42 wks.			.0006*
8203	30-33 wks.	.1395	.0434	.0242
	34-37 wks.		.4889	<.0001*
	38-42 wks.			<.0001*
6738	30-33 wks.	.0365	.1310	<.0001*
	34-37 wks.		.4755	<.0001*
	38-42 wks.			<.0001*
5468	30-33 wks.	.0134	.0034*	<.0001*
	34-37 wks.		.5430	<.0001*
	38-42 wks.			<.0001*
4443	30-33 wks.	.1408	.0327	.0107
	34-37 wks.		.3928	<.0001*
	38-42 wks.			<.0001*
3613	30-33 wks.	.0729	.0271	.0183
	34-37 wks.		.5890	<.0001*
	38-42 wks.			<.0001*
2978	30-33 wks.	.0888	.0142	.0006*
	34-37 wks.		.3350	<.0001*
	38-42 wks.			<.0001*
2441	30-33 wks.	.2229	.0462	<.0001*
	34-37 wks.		.3044	<.0001*
	38-42 wks.			<.0001*
2001	30-33 wks.	.2686	.2848	.0002*
	34-37 wks.		.9627	<.0001*
	38-42 wks.			<.0001*

(* Bonferroni-Dunn adjusted $p<0.0083$)

Table III.6 Differences between amplitude for four different age groups for each of the nine f_2 frequencies.

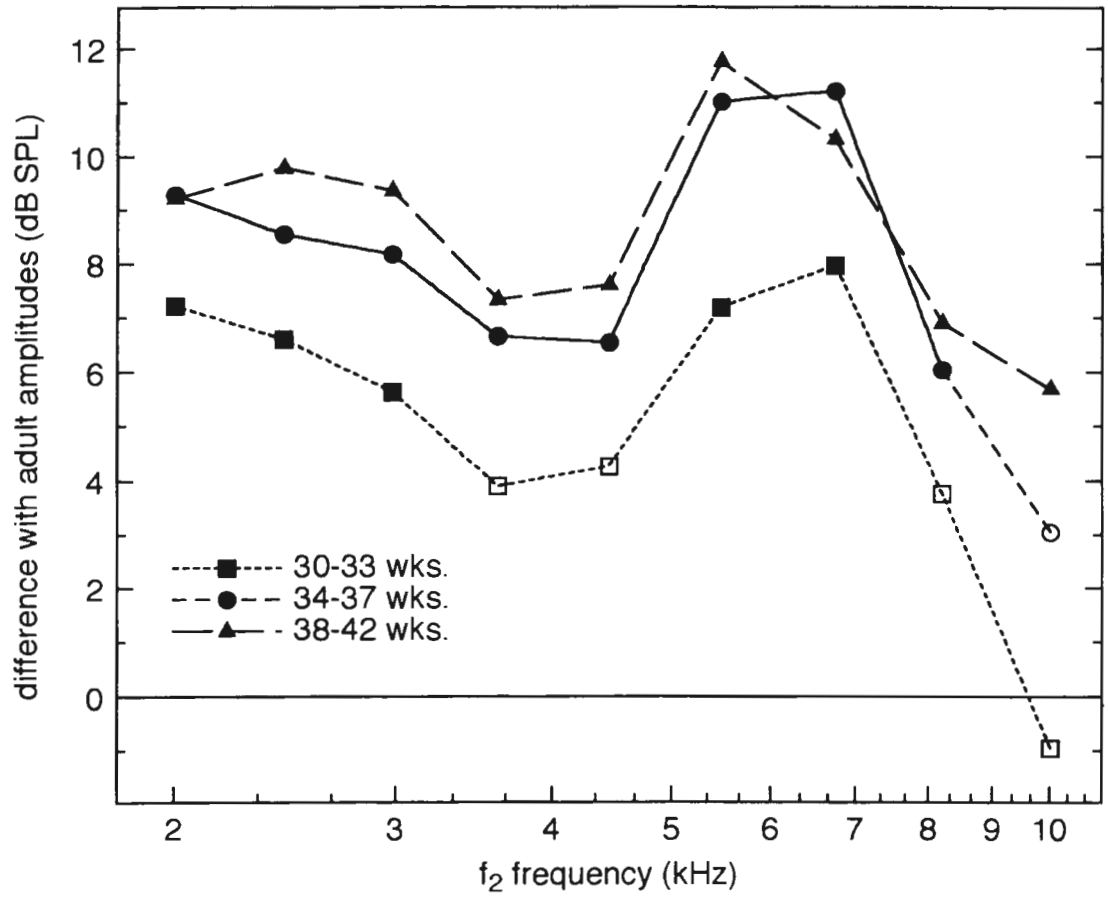


Figure 3.22 The differences between the adult amplitude and the young groups Note the significant differences (solid symbols are significant, open symbols are not significant) between the young groups and the adult groups.

Chapter 4. DISCUSSION

OVERVIEW

The purpose of this investigation was to study maturation of cochlear mechanics by using a pre-synaptic measure of cochlear function, namely DPEs. It was hoped that by comparing the cochlear travel times from groups of neonates, and term, and adults we may learn more about cochlear maturation from a pre-synaptic viewpoint. The present investigation expanded the scope of previous auditory development studies by using DPE phase measurements to calculate cochlear travel times over a large frequency range and for a very young subject population (30-33 weeks CA). The results from this study are summarized below.

1) The effect of intensity on the DPE phase-versus-frequency relationship was investigated in adults. The slope of the travel time-frequency function were found to decrease with intensity indicating shorter travel times for higher intensity primary tones.
2) Round-trip travel times were measured in four different age groups. These measurements showed that there are significant differences between the youngest preterms (30-33 weeks CA) and the other groups and between the older preterms (34-37 weeks CA) and the term-born (38-42 weeks CA) infants and the adults. There were however, no differences in travel times between the older preterms and the term-born (38-42 weeks CA) infants.
3) The present study extended the frequency range studied from 1.7 to 10 kHz in order to record the optimum f_2/f_1 ratio above 4 kHz. No significant effect of age was found across the four age groups. Although there was no affect of age on the optimum ratio, there was a significant difference across frequency. The optimum ratio becomes larger as the f_2 frequency decreases. There appears to be a natural break in the optimum ratio

between 3.5 and 4.9 kHz. It is at this point (approximately 4 kHz) where the ratio changes, above and below this point the ratios are significantly different from each other. The optimum ratio above $f_2 > 4$ kHz is smaller (1.18) than the ratio below $f_2 < 4$ kHz (1.22).

4) Emission amplitude was recorded across the frequency range from 2 to 10 kHz in all four age groups. The results showed that the adult amplitudes were much lower than the three neonate groups across the frequency range (except at 10 kHz). The amplitude of the emission increases as a function of age from the youngest preterm to the term group and then decreases until it reaches adults values. With the exception of the highest frequency (10 kHz), the neonatal emissions are 4 to 12 dB higher than those of the adult group.

Intensity and the DPE Phase-versus-Frequency Relationship

The effect of intensity on the DPE phase-versus-frequency relationship was investigated in the adult group. The means for each of the intensity series revealed shorter travel times for higher intensities. The slope of the travel time-frequency function were found to decrease with intensity. This is in agreement with previous reports by Kimberley et al. (1993) and Stover et al. (1994) who also reported a inverse relationship between travel time and intensity. This can be accounted for by a broadening of the tuning as the intensity of the primary tones increase. Ruggero and colleagues (1992, 1994) reported that the center of gravity of the time domain response of a portion of the BM for low intensity clicks reaches the maximum later in the live cochlea but for high intensity clicks the maximum is reached earlier. This suggests that the transport time will remain the same for all intensities but that the build-up time will shorten as stimulus intensity is increased.

It had previously been reported by others (Kimberley et al., 1993, Stover et al., 1994) that travel time increases as the primary tone levels decrease and that this increase was most noticeable in the lower frequencies. Dreisbach & Siegel (1995) in their investigation of the effect of calibrating with a microphone close to the tympanic membrane as opposed to at the probe placement (farther away from the tympanic membrane) found that the mean group delay measurement had less variation at the higher frequencies than at the lower frequencies. This suggests that variation, especially that found in the low frequencies, may be due to the distance that the microphone is away from the tympanic membrane and that there will be some difference between subjects based on the variation in distance from the microphone to the tympanic membrane.

DPE Phase-versus-Frequency Relationships Across Age Groups

This DPE phase-versus-frequency relationship was equated to round-trip travel times and compared for four different age groups. In order to determine maturation, the first step is to establish the round-trip travel times for adults. Figure 4.1 illustrates the travel times for the adult group and compares it with other studies. Kimberley et al. (1993), Stover et al. (1994) and Brown et al. (1995) investigated the phase-versus-frequency relationship for DPEs of various f_2 frequencies by holding f_2 constant and sweeping f_1 around it. The "swept-f_2" paradigm will give a longer travel time and therefore can not be used for this comparison. There is good agreement between the different investigations. They all show an inverse relationship between frequency and round-trip travel time.

As shown in Figure 4.2, the infant data of Brown et al. (1995) are compared with the data from this study although there is a large difference in the number of subjects. The differences in travel times are noted especially in the lower frequencies. Some of this difference may be accounted for by the difference in stimulus amplitude used. The

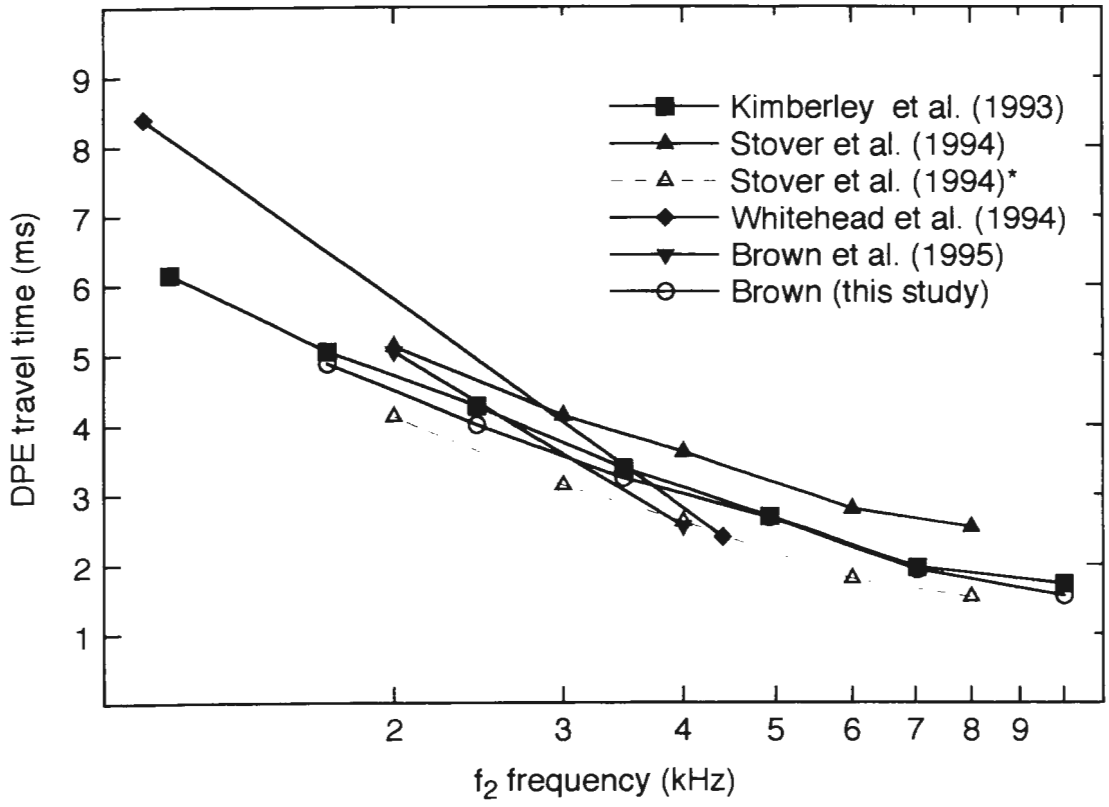


Figure 4.1 Comparison of adult DPE round-trip travel times from different studies.

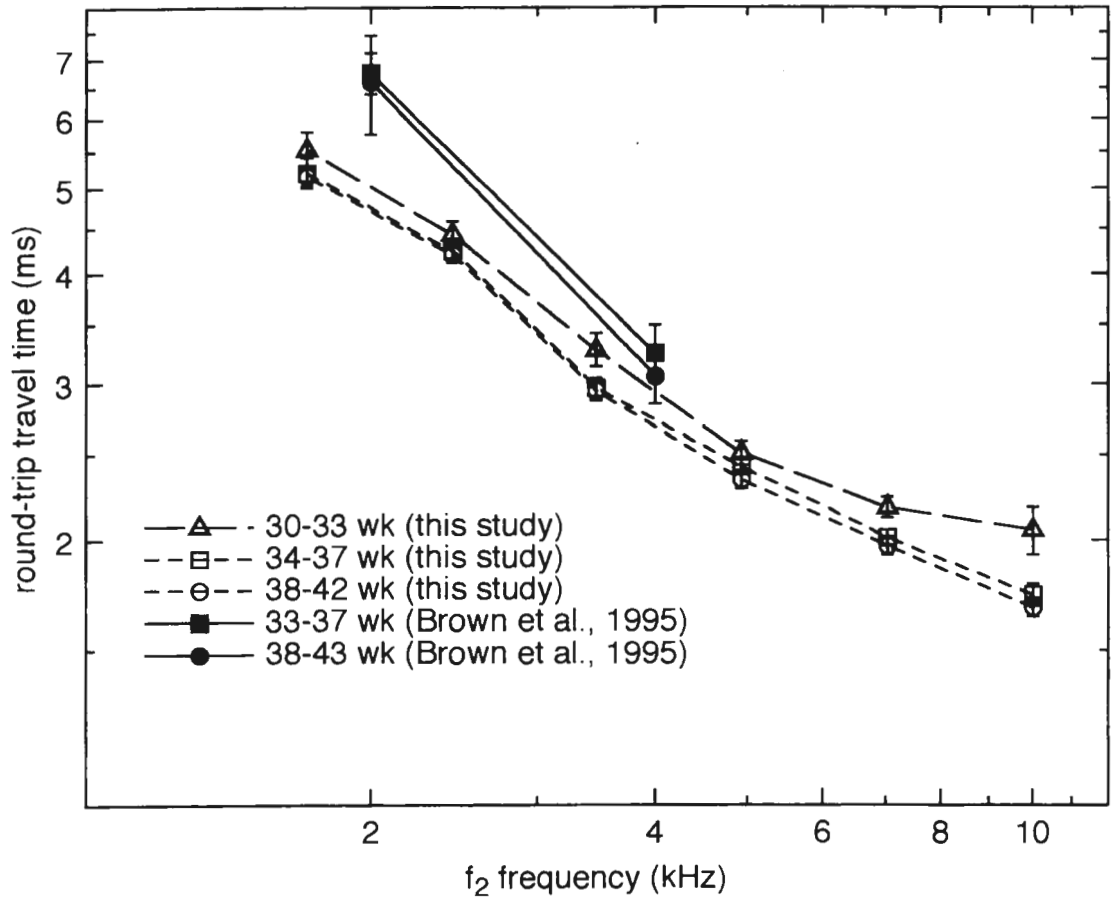


Figure 4.2 Comparison of neonate DPE round-trip travel times from different studies.

previous section found as much as 0.5 ms difference between the 40 (Brown et al., 1995) and 45 dB (present study) f_2 tone at the frequencies tested. Although they collapsed the two infant groups together, their data suggests no difference between these two age groups which is the same as in the present study. As reported previously the most variability appears to be in the lower frequencies and the most noticeable difference occurred in the higher frequency range. It is unfortunate that the high frequency range was not investigated by Brown et al. (1995).

The present study revealed significant differences in round-trip travel times between the youngest preterms (30-33 weeks CA) and the other groups, that there were no differences between the older preterms and the term-born (38-42 weeks CA) infants and that there were significant differences between these older infants and the adults. This corresponds to a previous study by Brown et al. (1995) which showed differences between infants and adults. This study investigated the differences in the mechanical response of the cochlea between infants and adults (Brown et al., 1995). Their results from a preterm group (33 - 38 wks. CA) and a term group (39-43 wks CA) were collapsed together to compare to an adult group. They reported a significant difference between the infants and the adults and suggest that this differences is at the cochlear level and not from either changes or development of the external or middle ear.

The difference in round-trip travel times between the different age groups in this study show that the delays for the infant groups are longer in the high and low frequencies but shorter in the mid-frequency range. This change in the mid-frequencies may be due to the differences seen by Dreisbach & Siegel (1995). If it is assumed that the microphone placement in the infant ear canal is much closer to the tympanic membrane than it is in the adult, it may be similar to the calibration done at the tympanic membrane. If the correction factor (difference from tympanic membrane calibration to probe calibration) from Dreisbach & Siegel (1995) is applied to the infant data as shown in Figure 4.3, then the youngest

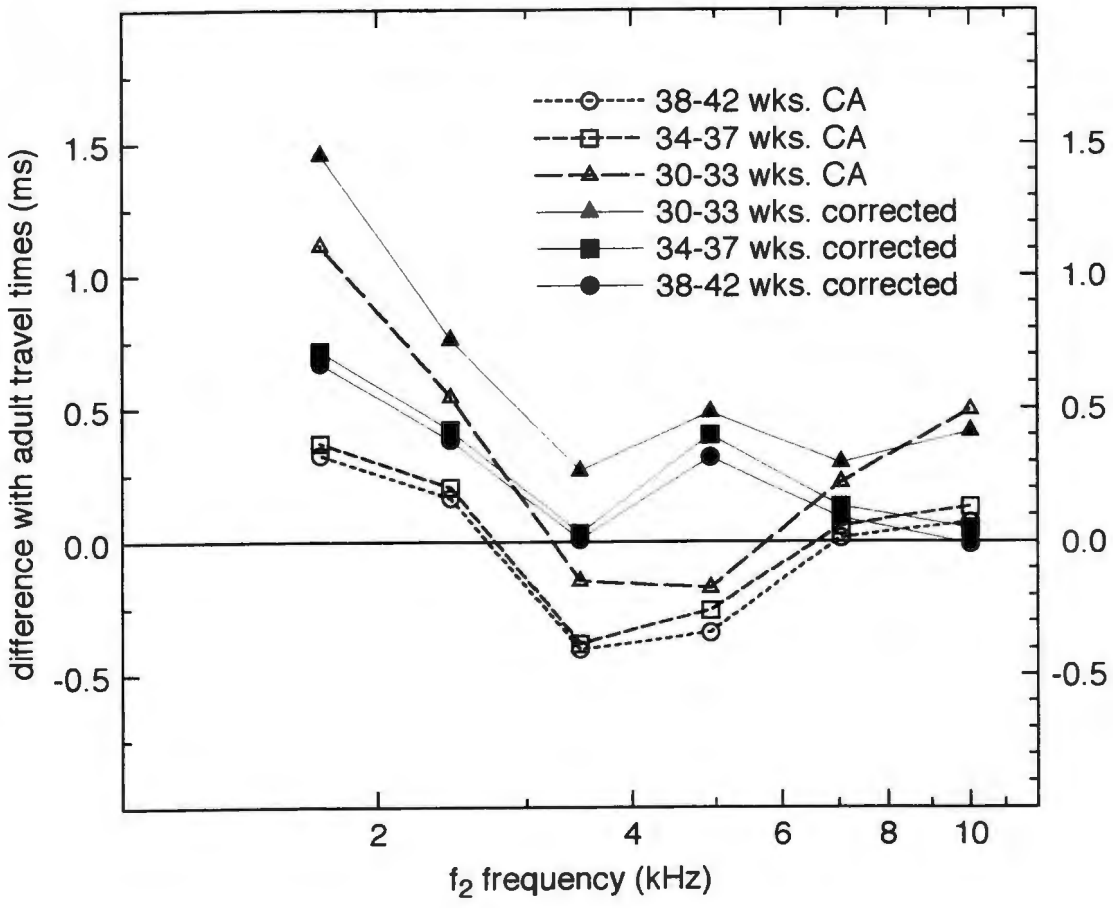


Figure 4.3 The difference between neonatal and adult travel times using the correction factor from Dreisbach & Siegel (1995).

preterm group has longer travel times and therefore has a greater difference than the other three groups. The delays of the other two infant groups (34-37 and 38-42 wks. CA) are increased in the mid-frequency range and decreased in the high frequencies. This correction adjusts the travel times so that the older infant groups are more adult-like, suggesting there is less of a difference between them. However, it now appears that there is a trend to decrease latency with age especially with the youngest preterm group. This situation may be explained by external and/or middle ear development or a conductive loss. Eggermont and Salamy (1988) reported a high incidence of conductive problems in preterm infants. Thus the amplitude of both the stimulus and the emission would be decreased. As revealed in this study, as the primary tones decrease the latency of the emission also decreases. If the differences in latency between the youngest preterms and the other neonates are compared to the intensity functions of the adults, the potential dB (conductive) loss can be calculated (see Figure 4.4). As this Figure shows, a loss of less than 10 dB can account for the difference in latency between these groups of neonates (except at 10 kHz where 27 dB is required). This could then account for the differences seen between the different age groups.

The results of the present investigation suggest that there may be some maturation in the cochlea occurring up until 34 weeks CA after which the cochlea is mature and functioning like that of the adult. This contradicts the conclusions from Eggermont et al. (1993), who found using derived-band ABRs that wave I latencies for high frequencies (5.7-11.3 kHz) reached adult values at 3-6 months of age and suggested that this was due to late cochlear maturation for the high frequencies. The difference between these two groups of data suggests that the cochlea is mature at term birth but that there is still synaptic maturation occurring which is measured in the ABR but not in the pre-synaptic DPE measurement.

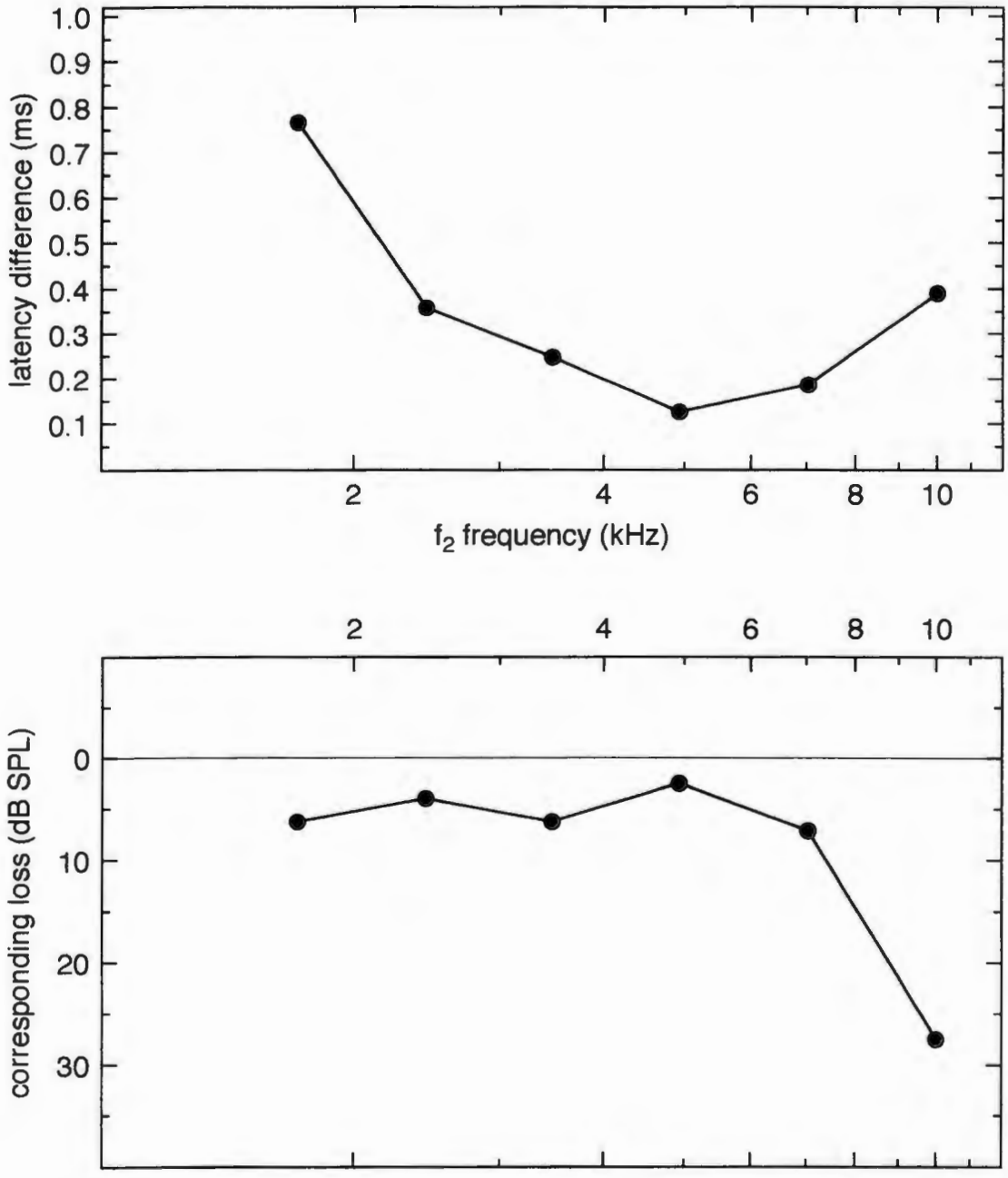


Figure 4.4 The latency difference between the youngest preterm (30-33 wks.) and the other neonates. This difference in latency may correspond to a loss in stimulus intensity between the two groups.

Optimum f_2/f_1 Ratios

The optimum f_2/f_1 ratio was investigated across age, frequency and intensity level. An early report on a small number of adult subjects had indicated that the optimum f_2/f_1 ratio was 1.25 (Kemp & Brown, 1983). This was considered to be the optimum ratio across the frequency range for DPE testing and subsequent studies also found very similar ratios (see Table I.2). Although this ratio was from studies in the adult, it was used as the f_2/f_1 ratio when testing infants. Lafreniere et al. (1991) suggested that the ratio may be optimum for adults but it has not been studied in infants. Brown et al. (1994) investigated the optimum f_2/f_1 ratio at 2 and 4 kHz in term-born infants and found the ratio to be 1.2 which was in agreement with the optimum ratio for adults. The present study extended the frequency range from 1.7 to 10 kHz and recorded the optimum f_2/f_1 ratio. No significant effect of age across the four age groups was found. This indicates that the ratio is stable and that maturation has no effect on it. This also suggests that cochlear excitation profiles, which are assumed to be responsible for that ratio are maturing early.

Although there was no effect of age on the optimum ratio, there was a significant difference across frequency. The ratio becomes larger as the f_2 frequency decreases. There appears to be a natural break in the optimum ratio between 3.5 and 4.9 kHz. It is at this point (approximately 4 kHz) where the ratio changes, above and below this point the ratios are significantly different from each other. The optimum ratio above $f_2 > 4$ kHz is smaller (1.18) than the ratio below $f_2 < 4$ kHz (1.22). Previous studies reported the optimum ratio to be approximately 1.2 for all frequencies. However, Harris et al. (1989) who reported an optimum ratio of 1.22, also noted that there was an inverse relationship between the optimal f_2/f_1 ratio and the frequency of the DPE. The ratios which created the largest emissions in their study were larger at 1 kHz than at 4 kHz similar to the effect seen in this study. This may be explained by the change in the shape of the excitation profiles along the BM. As indicated by tuning curves, the low frequencies are more broad tuned

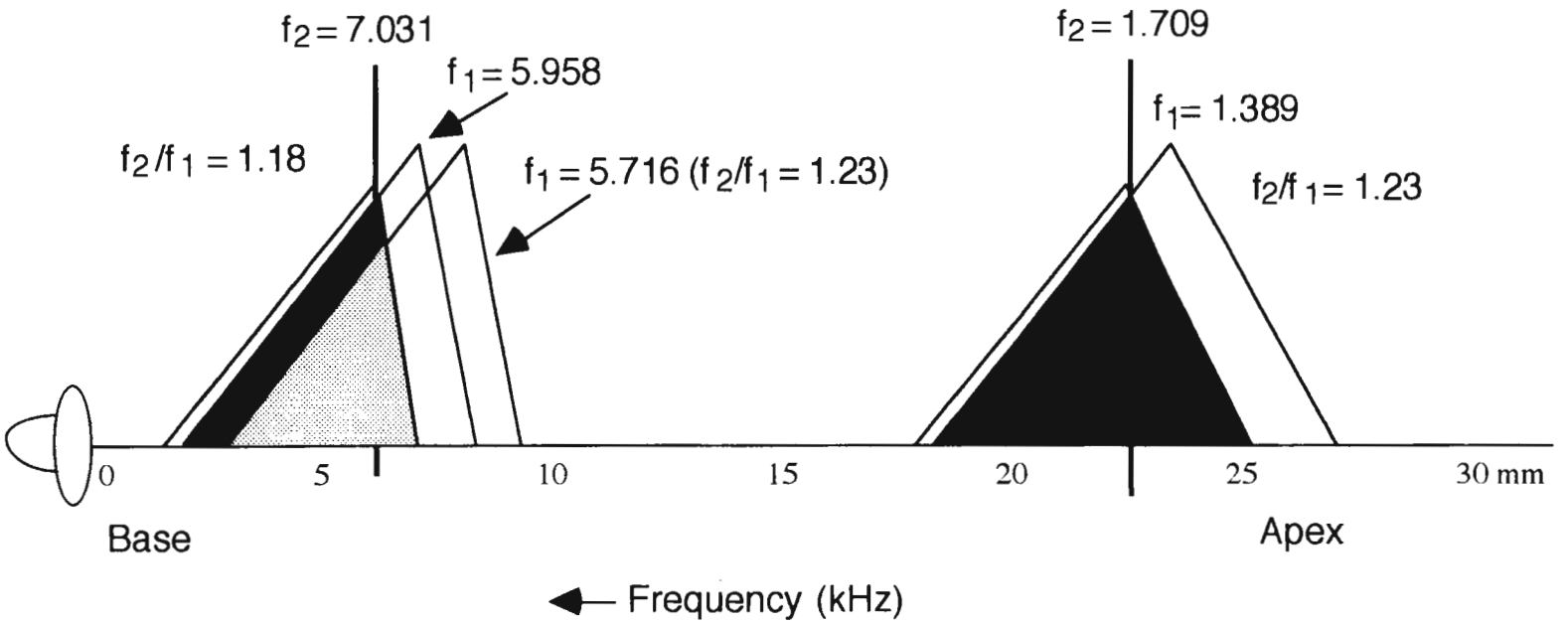


Figure 4.5 The optimum f_2/f_1 ratio is larger in the low frequencies than for high frequency primary tones. Note the change in slope at the apical end and the corresponding region of overlap of the BM associated with the optimum ratio for high and low frequencies. The high frequency primary tone obtains optimal overlap at a lower f_2/f_1 ratio, the f_1 tone for a ratio of 1.23 is also shown. The overlap associated with this one (shown in gray) is smaller, indicating the need for a different f_1 tone to generate the maximal overlap.

than high frequencies and change the slope of the profile at the apical end. The overlap on the BM associated with a particular ratio in the high frequencies will be different than in the low frequencies. As can be seen in Figure 4.5, the overlap associated with an optimum ratio at each end of the cochlea has a different profile due to this change in slope. The f_1 frequency which creates the optimum ratio will then be further apart in the lower frequencies than in the higher frequencies. This Figure also shows the decrease in overlap at the basal end as the ratio is increased. It can also be seen that if the ratio of the primary tones at the apical end were smaller the overlap may cause a suppression of the f_2 tone thereby reducing the emission.

Allen and Fahey (1993) estimated the optimum ratio for human data by a power curve fit which indicated an inverse relationship. As shown in Figure 4.6, their estimation of optimum ratio has the same trend as the present study, which is as the f_2 frequency decreased, the optimum ratio increased. However, their optimum ratio does not become as large in the low frequencies and the change in ratio does not show the break at approximately 4 kHz. Although there was no significant difference in optimal f_2/f_1 ratios across age groups where was a trend for the preterm and term infants to have larger ratios than the adults in this frequency region. This may have exaggerated the break at the mid-frequency region when collapsed across age groups. It is possible that the same effect which caused the mid-frequency range to have a shorter than expected travel time may also effect the optimal f_2/f_1 ratio. It could be suggested that the probe being closer to the ear drum in the infant may cause an increase in the sound pressure level of the primaries in this region. An increase in intensity of the primaries would cause the optimum f_2/f_1 ratio to increase as was seen in the infant data.

The effect of intensity on the optimum f_2/f_1 ratio was studied using the adult group. As intensity increases from low to high the optimum ratio also increases, this occurred at all but two frequencies (f_2 = 3.4 and 7.0 kHz). As the intensity of the primary tones increases

resulting in a broadening of the BM tuning, maximum overlap occurs at a lower f_1 frequency or a frequency further away from the f_2 frequency place. This occurs so that the maximum overlap will be maintained. There must be some balance for the two primary tones between overlap and suppression. Overlap of the two primary tones causes the largest non-linear interaction whereas suppression of one tone over another tends to reduce the importance of f_2 and also the emission. As shown in Figure 4.7, the decrease in intensity of the primary tones leads to a decrease in the overlap and in order to maintain the overlap the ratio would need to become smaller. One could also see that as the intensity of the tones increases the f_1 tone may overlap the f_2 tone and suppress the emission unless the optimal ratio is increased so that the f_1 tone moves further away from the f_2 tone.

Amplitude of the Emission

The amplitude of the emission can be measured using the "DP audiogram" method. This method sweeps across the frequency range at a constant intensity with fixed f2/f1 ratio and the amplitude of the resulting emission is plotted as a function of the f_2 frequency. The emission resulting from this method can be used to investigate the maturation of the cochlea. Using a standard testing protocol, the amplitude of the emission can be compared for both adult and infant. The results showed that the adult amplitudes were much lower than the three neonate groups across the frequency range (except at 10 kHz). There appears to be a developmental trend in the amplitude of the emission. The amplitude increases as a function of age from the youngest preterm to the term group and then decreases until it reaches adults values. With the exception of the highest frequency (10 kHz), the neonatal emissions are 4 to 12 dB higher than those of the adult group.

Lafreniere et al. (1991) and Brown et al. (1994) both compared the emission amplitude of infants and adults. Lafreniere et al. (1991) reported that the average DPE amplitude of the newborn was between 0.4 and 6.6 dB higher than adults. They also noted

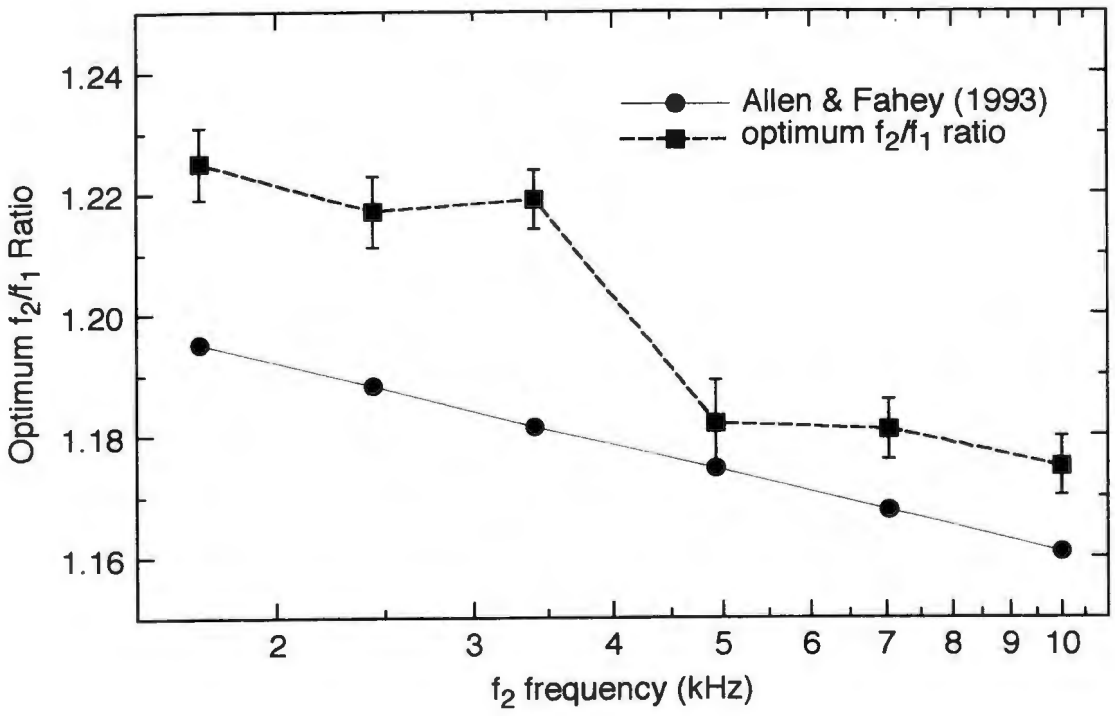


Figure 4.6 Comparison of optimum f_2/f_1 ratios.

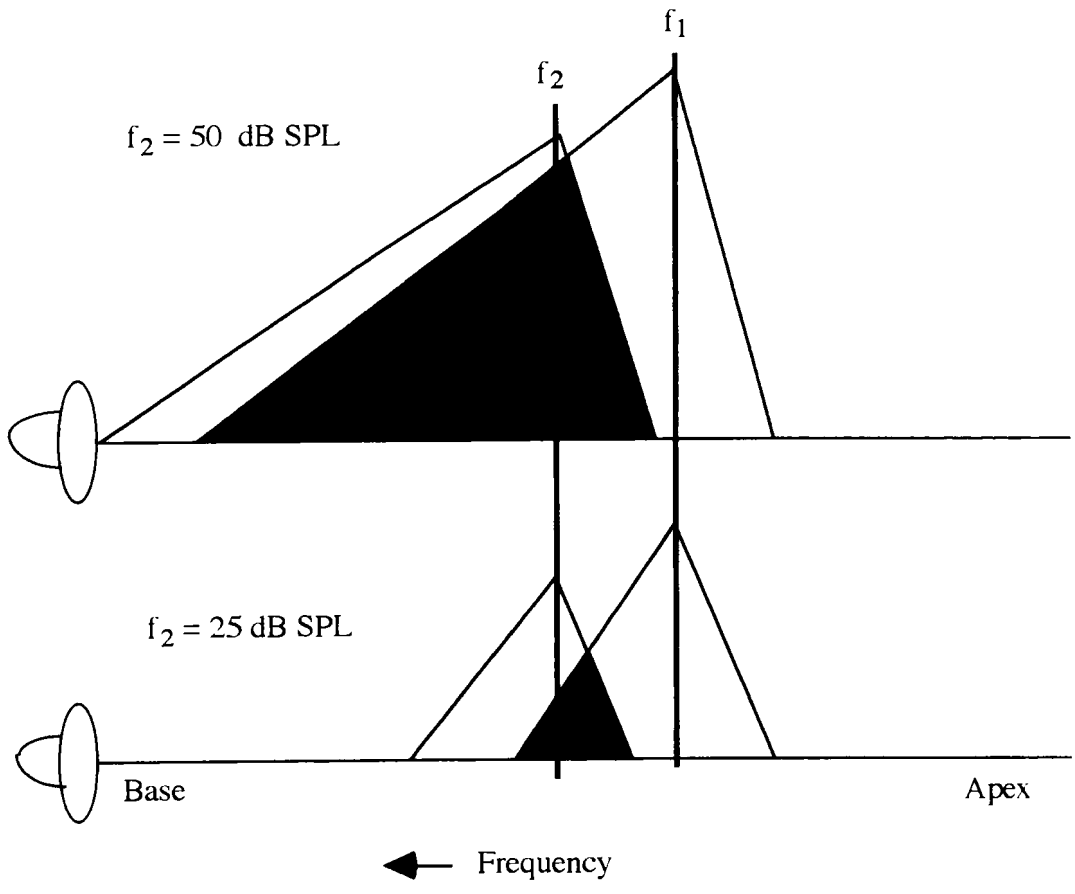


Figure 4.7 An apical shift of the region of overlap between f_2 and f_1 for decreasing stimulus intensity may contribute to the need for a change in optimal ratio.

a decrease in the difference of the emission in the high frequencies (8 kHz) similar to the trend found in the present study. Brown et al. (1994) found that the mean level of the DPE was higher in the infant group but that this difference was not significant. In another study, Brown et al. (1995) reported a significant difference at some frequencies between the neonates and the adults. However, they also found no significant difference between the 33-38 weeks CA group and the 39-43 weeks CA group. This is in good agreement with the present study.

There appears to be two changes happening, one between the youngest preterm (30-33 wks.) group and the term borns and the other between the term borns and the adults. This first change in amplitude of the emission suggests that there is some maturational development occurring between 30-33 weeks and term where the emission grows in amplitude. The growth in the amplitude may be due to some development in the external or middle ear system or a clearing of the middle ear (a simple disappearance of a conductive loss) which would allow for a better forward and reverse transduction of the primary tones and the emission. This is evident in the changes seen in a DP growth curve, as the stimulus is increased the resulting emission also increases. Changes in transmission of sound through the middle ear becomes more efficient and the loading of the cochlea changes so that the emission would have a larger amplitude. Therefore the differences in amplitude seen between preterm and term borns could be attributable to changes in the middle ear.

The amplitude of the emission decreased between the term borns and adults. This decrease in emission amplitude occurred at all frequencies including those below 2 kHz, therefore it can not be attributable to a standing wave issue. This difference in amplitude between term borns and adults is probably not due to the external or middle ear development, as one would expect changes in the middle ear to increase the amplitude of the emission. Results from Keefe et al.'s (1993) comparison of infant and adult ear canal

impedance and reflection coefficients further support a decrease in the emission amplitude for the infants, which is opposite to what was found. Therefore, this difference must be found in the cochlea. The question then becomes, is this decrease developmental or destructional, is the cochlea fully developed at birth and loses its function as it ages? The findings from this study are that the cochlear travel times are mature at birth which suggest that it is not developmental. In addition, Lonsbury-Martin et al. (1991a) reported that DPE amplitude decreased between 30 and 60 year of age. This suggests that there is a degradation of the cochlea (probably the outer hair cells) starting at birth and probably continuing through out one's life span.

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Appendicies

Appendix A

Unpaired T-test Results

10 kHz

Unpaired t-Test X_1: Age 1/2 Y_1: 10k - 1/2

DF:	Unpaired t Value:	Prob. (2-tail):
62	2.703	.0089

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	24	2.052	.625	.128
2	40	1.731	.325	.051

Unpaired t-Test X_2: Age 1/3 Y_2: 10k - 1/3

DF:	Unpaired t Value:	Prob. (2-tail):
62	3.369	.0013

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	24	2.052	.625	.128
3	40	1.675	.261	.041

Unpaired t-Test X_3: Age 1/4 Y_3: 10k - 1/4

DF:	Unpaired t Value:	Prob. (2-tail):
62	4.674	.0001

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	24	2.052	.625	.128
4	40	1.542	.231	.037

Unpaired t-Test X_4: Age 2/3 Y_4: 10k - 2/3

DF:	Unpaired t Value:	Prob. (2-tail):
78	.853	.3961

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	1.731	.325	.051
3	40	1.675	.261	.041

Unpaired t-Test X_5: Age 2/4 Y_5: 10k - 2/4

DF:	Unpaired t Value:	Prob. (2-tail):
78	3.002	.0036

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	1.731	.325	.051
4	40	1.542	.231	.037

Unpaired t-Test X_6: Age 3/4 Y_6: 10k - 3/4

DF:	Unpaired t Value:	Prob. (2-tail):
78	2.411	.0183

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
3	40	1.675	.261	.041
4	40	1.542	.231	.037

7k

Unpaired t-Test X_1: Age 1/2 Y_1: 7k - 1/2

DF:	Unpaired t Value:	Prob. (2-tail):
62	2.428	.0181

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	25	2.176	.289	.058
2	39	2.011	.251	.04

Unpaired t-Test X_2: Age 1/3 Y_2: 7k - 1/3

DF:	Unpaired t Value:	Prob. (2-tail):
63	2.767	.0074

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	25	2.176	.289	.058
3	40	1.969	.296	.047

Unpaired t-Test X_3: Age 1/4 Y_3: 7k - 1/4

DF:	Unpaired t Value:	Prob. (2-tail):
60	3.934	.0002

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	25	2.176	.289	.058
4	37	1.923	.218	.036

Unpaired t-Test X_4: Age 2/3 Y_4: 7k - 2/3

DF:	Unpaired t Value:	Prob. (2-tail):
77	.672	.5035

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	39	2.011	.251	.04
3	40	1.969	.296	.047

Unpaired t-Test X_5: Age 2/4 Y_5: 7k - 2/4

DF:	Unpaired t Value:	Prob. (2-tail):
74	1.626	.1081

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	39	2.011	.251	.04
4	37	1.923	.218	.036

4.9k

Unpaired t-Test X_1: Age 1/2 Y_1: 4k 1/2

DF:	Unpaired t Value:	Prob. (2-tail):
63	.947	.3475

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	25	2.506	.381	.076
2	40	2.421	.334	.053

Unpaired t-Test X_2: Age 1/3 Y_2: 4k - 1/3

DF:	Unpaired t Value:	Prob. (2-tail):
63	1.837	.071

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	25	2.506	.381	.076
3	40	2.338	.346	.055

Unpaired t-Test X_3: Age 1/4 Y_3: 4k - 1/4

DF:	Unpaired t Value:	Prob. (2-tail):
62	-1.787	.0787

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	25	2.506	.381	.076
4	39	2.664	.32	.051

Unpaired t-Test X_4: Age 2/3 Y_4: 4k - 2/3

DF:	Unpaired t Value:	Prob. (2-tail):
78	1.095	.277

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	2.421	.334	.053
3	40	2.338	.346	.055

Unpaired t-Test X_5: Age 2/4 Y_5: 4k - 2/4

DF:	Unpaired t Value:	Prob. (2-tail):
77	-3.301	.0015

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	2.421	.334	.053
4	39	2.664	.32	.051

Unpaired t-Test X_6: Age 3/4 Y_6: 4k - 3/4

DF:	Unpaired t Value:	Prob. (2-tail):
77	-4.351	.0001

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
3	40	2.338	.346	.055
4	39	2.664	.32	.051

3.4k

Unpaired t-Test X_1: Age 1/2 Y_1: 3k - 1/2

DF:	Unpaired t Value:	Prob. (2-tail):
61	2.145	.036

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	23	3.275	.679	.142
2	40	2.965	.465	.074

Unpaired t-Test X_2: Age 1/3 Y_2: 3k - 1/3

DF:	Unpaired t Value:	Prob. (2-tail):
61	2.246	.0283

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	23	3.275	.679	.142
3	40	2.944	.488	.077

Unpaired t-Test X_3: Age 1/4 Y_3: 3k - 1/4

DF:	Unpaired t Value:	Prob. (2-tail):
60	4.804	.0001

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	23	3.275	.679	.142
4	39	2.664	.32	.051

Unpaired t-Test X_4: Age 2/3 Y_4: 3k - 2/3

DF:	Unpaired t Value:	Prob. (2-tail):
78	.206	.837

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	2.965	.465	.074
3	40	2.944	.488	.077

Unpaired t-Test X_5: Age 2/4 Y_5: 3k - 2/4

DF:	Unpaired t Value:	Prob. (2-tail):
77	3.345	.0013

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	2.965	.465	.074
4	39	2.664	.32	.051

Unpaired t-Test X_6: Age 3/4 Y_6: 3k - 3/4

DF:	Unpaired t Value:	Prob. (2-tail):
77	2.999	.0037

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
3	40	2.944	.488	.077
4	39	2.664	.32	.051

2.4k

Unpaired t-Test X_1: Age 1/2 Y_1: 2k - 1/2

DF:	Unpaired t Value:	Prob. (2-tail):
61	.926	.3579

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	23	4.43	.711	.148
2	40	4.244	.796	.126

Unpaired t-Test X_2: Age 1/3 Y_2: 2k - 1/3

DF:	Unpaired t Value:	Prob. (2-tail):
61	1.344	.184

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	23	4.43	.711	.148
3	40	4.205	.598	.095

Unpaired t-Test X_3: Age 1/4 Y_3: 2k - 1/4

DF:	Unpaired t Value:	Prob. (2-tail):
61	2.491	.0155

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	23	4.43	.711	.148
4	40	4.002	.623	.099

Unpaired t-Test X_4: Age 2/3 Y_4: 2k - 2/3

DF:	Unpaired t Value:	Prob. (2-tail):
78	.253	.8013

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	4.244	.796	.126
3	40	4.205	.598	.095

Unpaired t-Test X_5: Age 2/4 Y_5: 2k - 2/4

DF:	Unpaired t Value:	Prob. (2-tail):
78	1.516	.1336

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	40	4.244	.796	.126
4	40	4.002	.623	.099

Unpaired t-Test X_6: Age 3/4 Y_6: 2k - 3/4

DF:	Unpaired t Value:	Prob. (2-tail):
78	1.482	.1423

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
3	40	4.205	.598	.095
4	40	4.002	.623	.099

1.7k

Unpaired t-Test X_1: Age 1/2 Y_1: 1k - 1/2

DF:	Unpaired t Value:	Prob. (2-tail):
29	.745	.4621

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	6	5.533	.651	.266
2	25	5.203	1.029	.206

Unpaired t-Test X_2: Age 1/3 Y_2: 1k - 1/3

DF:	Unpaired t Value:	Prob. (2-tail):
40	1.063	.294

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	6	5.533	.651	.266
3	36	5.156	.825	.137

Unpaired t-Test X_3: Age 1/4 Y_3: 1k - 1/4

DF:	Unpaired t Value:	Prob. (2-tail):
44	2.484	.0169

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
1	6	5.533	.651	.266
4	40	4.877	.598	.094

Unpaired t-Test X_4: Age 2/3 Y_4: 1k - 2/3

DF:	Unpaired t Value:	Prob. (2-tail):
59	.199	.8428

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	25	5.203	1.029	.206
3	36	5.156	.825	.137

Unpaired t-Test X_5: Age 2/4 Y_5: 1k -2/4

DF:	Unpaired t Value:	Prob. (2-tail):
63	1.62	.1102

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
2	25	5.203	1.029	.206
4	40	4.877	.598	.094

Unpaired t-Test X_6: Age 3/4 Y_6: 1k - 3/4

DF:	Unpaired t Value:	Prob. (2-tail):
74	1.701	.0931

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
3	36	5.156	.825	.137
4	40	4.877	.598	.094

Appendix B

30 - 33 weeks
Comparison between L1-L2 of 10 and 15 dB

Unpaired t-Test X_1: Level diff Y_1: 10009.8

DF:	Unpaired t Value:	Prob. (2-tail):
20	-.229	.8216

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	18	-3.437	8.719	2.055
Group 2	4	-2.369	6.758	3.379

Unpaired t-Test X_1: Level diff Y_2: 8203.13

DF:	Unpaired t Value:	Prob. (2-tail):
23	.371	.7144

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	18	3.244	7.297	1.72
Group 2	7	2.151	4.133	1.562

Unpaired t-Test X_1: Level diff Y_3: 6738.28

DF:	Unpaired t Value:	Prob. (2-tail):
23	1.34	.1932

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	18	6.56	6.733	1.587
Group 2	7	2.65	5.999	2.267

Unpaired t-Test X_1: Level diff Y_4: 5468.75

DF:	Unpaired t Value:	Prob. (2-tail):
23	.895	.38

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	18	3.725	7.877	1.857
Group 2	7	.924	3.646	1.378

Unpaired t-Test X_1: Level diff Y_5: 4443.36

DF:	Unpaired t Value:	Prob. (2-tail):
22	1.564	.1321

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	17	3.076	7.49	1.817
Group 2	7	-1.715	4.585	1.733

Unpaired t-Test X_1: Level diff Y_6: 3613.28

DF:	Unpaired t Value:	Prob. (2-tail):
23	.688	.4985

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	18	2.579	7.108	1.675
Group 2	7	.614	3.813	1.441

Unpaired t-Test X_1: Level diff Y_7: 2978.52

DF:	Unpaired t Value:	Prob. (2-tail):
23	-.506	.6175

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	18	2.725	7.777	1.833
Group 2	7	4.303	4.034	1.525

Unpaired t-Test X_1: Level diff Y_8: 2441.41

DF:	Unpaired t Value:	Prob. (2-tail):
18	.264	.795

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	15	6.015	6.755	1.744
Group 2	5	5.167	3.891	1.74

Unpaired t-Test X_1: Level diff Y_9: 2001.95

DF:	Unpaired t Value:	Prob. (2-tail):
15	1	.3332

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	11	10.603	8.131	2.451
Group 2	6	7.069	3.636	1.484

Unpaired t-Test X_1: Level diff Y_{10}: 1660.16

DF:	Unpaired t Value:	Prob. (2-tail):
12	1.173	.2637

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	9	14.013	5.469	1.823
Group 2	5	10.667	4.324	1.934

Unpaired t-Test X_1: Level diff Y_{11}: 1318.36

DF:	Unpaired t Value:	Prob. (2-tail):
6	3.191	.0188

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	6	12.785	3.639	1.486
Group 2	2	3.348	3.531	2.497

A group contains no values for 1074.22 Hz. This statistic can not be computed for Column X(1)-Column Y(12).

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	4.961	6.256	1.162
Group 2	23	5.546	6.493	1.354

Unpaired t-Test X_1: Level diff Y_3: 6738.28

DF:	Unpaired t Value:	Prob. (2-tail):
50	.253	.8009

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	8.862	4.857	.902
Group 2	23	8.527	4.591	.957

A group contains no values for 1074.22 Hz. This statistic can not be computed for Column X(1)-Column Y(12).

34 - 37 weeks
Comparison between L1-L2 of 10 and 15 dB

Unpaired t-Test X_1: Level diff Y_1: 10009.8

DF:	Unpaired t Value:	Prob. (2-tail):
43	-.97	.3376

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	26	-.042	6.975	1.368
Group 2	19	1.824	5.435	1.247

Unpaired t-Test X_1: Level diff Y_2: 8203.13

DF:	Unpaired t Value:	Prob. (2-tail):
50	-.329	.7436

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	4.961	6.256	1.162
Group 2	23	5.546	6.493	1.354

Unpaired t-Test X_1: Level diff Y_3: 6738.28

DF:	Unpaired t Value:	Prob. (2-tail):
50	.253	.8009

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	8.862	4.857	.902
Group 2	23	8.527	4.591	.957

Unpaired t-Test X_1: Level diff Y_4: 5468.75

DF:	Unpaired t Value:	Prob. (2-tail):
50	1.054	.297

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	7.464	5.907	1.097
Group 2	23	5.853	4.866	1.015

Unpaired t-Test X_1: Level diff Y_5: 4443.36

DF:	Unpaired t Value:	Prob. (2-tail):
50	1.671	.1011

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	5.211	6.361	1.181
Group 2	23	2.391	5.623	1.172

Unpaired t-Test X_1: Level diff Y_6: 3613.28

DF:	Unpaired t Value:	Prob. (2-tail):
50	1.697	.096

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	5.957	6.331	1.176
Group 2	23	3.291	4.58	.955

Unpaired t-Test X_1: Level diff Y_7: 2978.52

DF:	Unpaired t Value:	Prob. (2-tail):
50	.067	.9471

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	29	5.765	6.664	1.237
Group 2	23	5.656	4.626	.965

Unpaired t-Test X_1: Level diff Y_8: 2441.41

DF:	Unpaired t Value:	Prob. (2-tail):
47	-.355	.7244

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	28	7.495	6.016	1.137
Group 2	21	8.064	4.872	1.063

Unpaired t-Test X_1: Level diff Y_9: 2001.95

DF:	Unpaired t Value:	Prob. (2-tail):
46	.095	.9245

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	28	11.489	6.957	1.315
Group 2	20	11.303	6.286	1.406

Unpaired t-Test X_1: Level diff Y_{10}: 1660.16

DF:	Unpaired t Value:	Prob. (2-tail):
38	1.701	.0971

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	21	14.828	7.25	1.582
Group 2	19	11.669	3.771	.865

Unpaired t-Test X_1: Level diff Y_{11}: 1318.36

DF:	Unpaired t Value:	Prob. (2-tail):
19	2.712	.0138

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	13	14.428	5.006	1.388
Group 2	8	9.103	2.98	1.053

Unpaired t-Test X_1: Level diff $Y_{1\,2}$: 1074.22

DF:	Unpaired t Value:	Prob. (2-tail):
10	2.974	.0139

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	6	16.983	2.07	.845
Group 2	6	7.482	7.546	3.081

38 - 42 weeks
Comparison between L1-L2 of 10 and 15 dB

Unpaired t-Test X_1: Level diff Y_1: 10009.8

DF:	Unpaired t Value:	Prob. (2-tail):
41	-1.372	.1776

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	10	1.466	3.42	1.082
Group 2	33	3.987	5.469	.952

Unpaired t-Test X_1: Level diff Y_2: 8203.13

DF:	Unpaired t Value:	Prob. (2-tail):
48	-.696	.4897

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	10	5.169	4.826	1.526
Group 2	40	6.317	4.626	.731

Unpaired t-Test X_1: Level diff Y_3: 6738.28

DF:	Unpaired t Value:	Prob. (2-tail):
48	2.432	.0188

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	10	11.755	4.212	1.332
Group 2	40	6.834	6.018	.951

Unpaired t-Test X_1: Level diff Y_4: 5468.75

DF:	Unpaired t Value:	Prob. (2-tail):
48	2.46	.0176

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	10	11.099	4.742	1.5
Group 2	40	6.609	5.255	.831

Unpaired t-Test X_1: Level diff Y_5: 4443.36

DF:	Unpaired t Value:	Prob. (2-tail):
48	2.279	.0272

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	10	8.569	6.432	2.034
Group 2	40	4.14	5.258	.831

Unpaired t-Test X_1: Level diff Y_6: 3613.28

DF:	Unpaired t Value:	Prob. (2-tail):
48	1.918	.061

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	10	8.702	7.263	2.297
Group 2	40	4.636	5.662	.895

Unpaired t-Test X_1: Level diff Y_7: 2978.52

DF:	Unpaired t Value:	Prob. (2-tail):
47	2.305	.0256

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	9	11.101	8.848	2.949
Group 2	40	5.948	5.309	.839

Unpaired t-Test X_1: Level diff Y_8: 2441.41

DF:	Unpaired t Value:	Prob. (2-tail):
48	1.517	.1357

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	10	11.494	6.306	1.994
Group 2	40	8.343	5.768	.912

Unpaired t-Test X_1: Level diff Y_9: 2001.95

DF:	Unpaired t Value:	Prob. (2-tail):
45	1.964	.0558

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	7	15.175	6.376	2.41
Group 2	40	10.679	5.457	.863

Unpaired t-Test X_1: Level diff Y_{10}: 1660.16

DF:	Unpaired t Value:	Prob. (2-tail):
39	1.967	.0563

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	4	16.231	5.45	2.725
Group 2	37	10.67	5.365	.882

Unpaired t-Test X_1: Level diff Y_{11}: 1318.36

DF:	Unpaired t Value:	Prob. (2-tail):
35	1.468	.1509

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	5	11.765	7.761	3.471
Group 2	32	8.017	4.902	.867

Unpaired t-Test X_1: Level diff Y_{12}: 1074.22

DF:	Unpaired t Value:	Prob. (2-tail):
27	2.409	.0231

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Group 1	3	17.898	5.446	3.144
Group 2	26	8.834	6.225	1.221

Appendix C

Regression Coefficients
10k ratio vs. f1 Intensity

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1.101	.018	1.101	60.962	<.0001
f1 Intensity	1.008E-3	3.292E-4	.241	3.061	.0026

Regression Coefficients
7k ratio vs. f1 Intensity

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1.133	.018	1.133	63.165	<.0001
f1 Intensity	5.335E-4	3.289E-4	.127	1.622	.1067

Regression Coefficients
4.9k ratio vs. f1 Intensity

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1.123	.025	1.123	45.360	<.0001
f1 Intensity	1.277E-3	4.509E-4	.226	2.832	.0053

Regression Coefficients
3.4k ratio vs. f1 Intensity

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1.207	.019	1.207	61.986	<.0001
f1 Intensity	-6.619E-5	3.596E-4	-.014	-.184	.8542

Regression Coefficients
2.4k ratio vs. f1 Intensity

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1.089	.024	1.089	45.855	<.0001
f1 Intensity	2.002E-3	4.405E-4	.313	4.543	<.0001

Regression Coefficients
1.7k ratio vs. f1 Intensity

	Coefficient	Std. Error	Std. Coeff.	t-Value	P-Value
Intercept	1.089	.022	1.089	49.343	<.0001
f1 Intensity	2.357E-3	4.101E-4	.370	5.748	<.0001