A comparative study of distortion-product-otoacoustic-emission fine structure in human newborns and adults with normal hearing

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Distortion product otoacoustic emissions (DPOAE) measured in human newborns are not adult-like. More than a decade of work from various investigators has created a well-developed body of evidence describing these differences but the putative anatomy or physiology has only been partially explained. Recently, Abdala and Keefe [J. Acoust. Soc. Am. **120**, 3832–3842 (2006)] have identified outer and middle ear immaturities that at least partially describe the differences observed between newborn and adult input–output functions and suppression tuning curves. DPOAE fine structure characteristics and their maturation have not been examined to any extent in the literature. Fine structure characteristics in two groups of ten newborns and young adults with normal hearing sensitivity are compared here. Consistent with previous reports, the newborns show higher DPOAE levels; greater fine structure depth and wider fine structure spacing is also observed in the newborns. Differences in fine structure morphology are also observed between the two age groups. While some of these findings are attributable to an immature outer and middle ear system in the newborns, it is argued that some observed differences in fine structure characteristics might be due to remnant immaturities in passive motion of the basilar membrane in the newborn cochlea.
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I. INTRODUCTION

Otoacoustic emissions (OAEs) are sounds generated in the inner ear that can be recorded in the ear canal (Kemp, 1978). When evoked using two simultaneous pure tones, distortion product (DP) OAEs can be recorded at frequencies mathematically related to the stimulus frequencies (Kemp, 1979a). The DPOAE at the frequency $2f_1-f_2$ (f_1 and f_2 represent the frequencies of the stimulus tones, $f_2>f_1$) is the most commonly studied and used clinically for detection of hearing loss (e.g., Dorn *et al.*, 1999). Although DPOAEs are widely used as a noninvasive assay in studying various aspects of peripheral auditory physiology and biophysics, our particular interest here is in their use as a tool to investigate maturation of the auditory periphery in humans (Abdala, 1998, 2001a, b, 2003; Abdala and Chatterjee, 2003; Abdala, 2004; Abdala and Keefe, 2006; Keefe and Abdala, 2007) as well as laboratory animals (Mills, 2004).

A. DPOAEs to study maturation of auditory peripheral function

A decade of work from various laboratories has found that DPOAE-based measures of cochlear function are not completely adult-like in human infants (Brown *et al.*, 1994; Abdala, 1998; Lasky, 1998; Abdala, 2001b, 2004). Brown and colleagues (1994) reported immature cochlear filtering in newborns at 4000 Hz, as measured by DPOAE f_2/f_1-ratio functions. DPOAE input/output (I/O) functions are not adult-like in infants either, and show immature saturation characteristics (Lasky, 1998; Abdala, 2000). DPOAE ipsilateral suppression tuning curves (STCs) at $f_2=6$ kHz have been found to be non-adult-like in very premature infants (30 weeks, postconceptional age), term-born infants and older infants through 6 months of age (Abdala *et al.*, 1996; Abdala, 1998, 2004; Abdala *et al.*, 2007). Typically, infant DPOAE STCs are significantly narrower in width, steeper on the low-frequency flank and have a sharper tip region than adult STCs. Additionally, the growth of DPOAE suppression (for low-frequency suppressor tones only) is shallower for infants than adults.

Clearly, DPOAE-based measures of peripheral auditory function recorded from infants are not adult-like in the high-frequency range (4–6 kHz) and they remain immature well into the post-natal period. The source(s) of these immaturities has not been fully specified, although recent evidence suggests that immaturities in the outer and middle ear system contribute significantly to the non-adult-like DPOAE features observed in human infants (Abdala and Keefe, 2006; Keefe and Abdala, 2007). It is not clear whether cochlear or medial olivocochlear sources contribute to the residual immaturities not attributable to the outer and middle ear system. Relatively recent confirmation that the DPOAE is comprised of multiple components arising from different

locations in the cochlea, provides yet another paradigm to study maturation of auditory peripheral function in humans.

B. DPOAE fine structure and components

The observation of a pseudo-periodic pattern of alternating maxima and minima in high-resolution recordings of DPOAEs, now known as fine structure, led to the initial prediction that the ear-canal DPOAE was comprised of more than one component (Kim, 1980). Following extensive theoretical and experimental work, the "two-source" model of DPOAEs is now well accepted for DPs where the characteristic frequency (CF) region is apical to that of the stimulus tones. In brief, for DPOAEs with CF regions on the basilar membrane apical to those of stimulus tones (i.e., $f_2 > f_1 > f_{dp}$), the initial DPOAE energy is generated in the overlap region between the traveling wave patterns evoked by the stimulus tones. This initial distortion energy is distributed bidirectionally with a portion propagating outwards to the ear canal and another portion propagating inwards (toward the apex of the cochlea). This second, inward propagating portion of the distortion energy reaches its CF region, is arguably affected by active physiological elements of the cochlea locally, and is returned to the ear canal as a second DPOAE component. The "interference" created by this second component and its impact (constructive or destructive) on DPOAE level can be observed in DPOAE fine structure patterns. The reader is directed to other sources for analytic treatments of this model of DPOAE generation (Talmadge *et al.*, 1998; Mauermann *et al.*, 1999a, b; Talmadge *et al.*, 1999).

Confirmation of two DPOAE components from two disparate locations in the cochlea comes from a variety of experiments. A suppressor of appropriate magnitude placed in close proximity to the $2f_1-f_2$ CF region eliminates/alters the component from this region, thereby reducing its contribution to the ear canal DPOAE and eliminating fine structure (Heitmann *et al.*, 1998; Talmadge *et al.*, 1999; Dhar and Shaffer, 2004). Fine structure is also eliminated when the CF region but not the overlap region falls in an audiometric notch, or region of hearing loss (Mauermann *et al.*, 1999b); the overlap component remains unaffected but the interference is eliminated due to the absence of a second component from the DP CF region. Finally, interference between the two components is also evident in time domain recordings when one stimulus tone is pulsed to alternately turn DPOAE generation on and off (Talmadge *et al.*, 1999). As the stimulus is turned on, the overlap component is recorded in isolation in the ear canal for a brief duration, whereas the second component travels to the DP CF region and is returned from there with a finite time delay compared to the component from the overlap region. By choosing the appropriate phase relationship between the two components, a cancellation notch can be observed in the ear canal at either signal onset or offset.

The DPOAE components from the overlap and DP CF regions have also been classified as *wave* and *place* fixed emissions (Knight and Kemp, 2000, 2001), as well as *nonlinear* and *reflection* components (Shera and Guinan, 1999; Shera and Zweig, 1991). Each of these models proposes a different mechanism of OAE generation and backward propagation. The mechanism notwithstanding, the presence of two (or more) DPOAE components in the ear canal signal is well established and accepted today.

The individual characteristics of these DPOAE components as a function of stimulus frequency ratio (Knight and Kemp, 2001; Dhar *et al.*, 2005) and stimulus level (Konrad-Martin *et al.*, 2001) have been of recent interest. The differential vulnerability of these two components has also been examined to a limited extent (Engdahl and Kemp, 1996). However the *developmental* aspects of DPOAE components and fine structure characteristics have remained largely unexplored. Here we report on a comparison of DPOAE components and their interaction, between human newborn and adult ears, as assessed by the fine structure of the ear canal DPOAE signal. To the best of our knowledge, such a comparison is not available in the peer-reviewed literature as of this writing.

II. METHODS

A comparison of DPOAE fine structure characteristics across two sets of independently recorded data is presented here. DPOAEs in ten newborns were recorded at the House Ear Institute in Los Angeles, California, whereas the results from ten young adults between the ages of 18 and 24 years were recorded at Northwestern University in Evanston, Illinois. The two data sets were recorded in accordance with the institutional review board regulations at the respective institutions and each data set was thoroughly de-identified before sharing with outside research personnel. In the following we provide separate descriptions of hardware, software for data recording, and initial estimation of DPOAE level and phase for each data set. The common analyses used to extract DPOAE fine structure parameters from both data sets are described as well.

A. Newborn data set

Ten term-born, normal-hearing human infants (mean gestational age at birth=38.6 weeks) served as subjects in this study, following acquisition of informed parental consent. They were tested within 72 h after birth. Nine left and one right ear were tested from five male and five female newborns with an average birth weight of 3200 g. Infants were wheeled in open isolettes from the mother's postpartum room to the Infant Auditory Research Laboratory in Women's and Children's Hospital, University of Southern California, Los Angeles County (USC+LAC). They were fed and changed if necessary prior to testing and once asleep, the DPOAE probe was placed at the entrance of the ear canal for testing.

A custom-designed DPOAE acquisition system (SuprDP) was used to generate stimuli and acquire data under the control of custom software using a 48 000 Hz sampling rate. The data acquisition hardware was based on an audio processor module developed by The House Ear Institute Engineering Department. The hardware includes two-channel D/A, two-channel A/D and a digital-signal processor (all 24-bit) as well as an analog high-pass filter (12 dB/oct.; 700 Hz

high-pass cutoff; note that this affected three data points where the DPOAE frequency was below 700 Hz). The data acquisition system was connected to an Etymotic Research ER-10C probe microphone. The ER-10C contains two output transducers and a low-noise microphone. The two stimulus tones were generated by the DSP processor and presented to the infants' ear canals using separate transducers. The microphone signal was high-pass filtered before being sampled by the A/D converter.

Twenty sweeps of the microphone signal were averaged by the DSP processor and comprised one block of data. Sweeps were accepted into a block only when the estimated root-mean-squared level in that sweep did not exceed a user-controlled artifact rejection threshold. Additionally, a block of data could be rejected by the user if the mean noise floor was >0 dB. A data point was eliminated automatically if a spike in noise occurred (defined ≥15 dB increase in noise from one point to an adjacent point) and SNR was <10 dB. A minimum of 6 and a maximum of 12 acceptable blocks of data were averaged to compute the final DPOAE amplitude or the DPOAE grand average. DPOAE level and phase were extracted from recordings using fixed stimulus levels of 65–55 dB SPL ($L_1 > L_2$) and f_2/f_1 ratio of 1.2. These stimulus parameters were used for both the newborn and adult groups as they are typically used in the clinic and may not be optimized for measuring the most robust fine structure in either group. For a first attempt at examining fine structure in human infants, moderate-low level of stimuli were used (rather than very low levels that might have enhanced fine structure), in order to produce robust DPOAE levels and sufficient signal-to-noise ratio (SNR) to observe an unequivocal response. DPOAEs were recorded between f_2 frequencies of 996–4020 Hz in 11.7 Hz intervals.

Intermodulation distortion produced by the recording system at $2f_1-f_2$ was on average, −25 dB SPL. The recording system mean noise floor ranged between −23 and −30 dB SPL. An *in situ* calibration procedure was conducted on both output transducers before each subject was tested. A chirp tone (swept-frequency signal from 10 to 10 000 Hz) with fixed voltage was presented to the transducer and the resulting SPL recorded in the ear canal. Based on this information, an equalization of output levels was performed for each subject to achieve target stimulus levels across test frequencies.

B. Adult data set

Individuals responding to advertisement fliers on the campus of Northwestern University in Evanston, Illinois were screened for inclusion in the experiment. Individuals, with hearing thresholds better than 20 dB HL (ANSI, 1996) between 0.25 and 8 kHz, negative history of otologic disease and noise exposure, and normal middle ear function indicated by a type A tympanogram, defined by static compliance between 0.4 and 1.5 cm^3 and peak pressure between ±150 daPa were included for detailed DPOAE recordings.

Signal generation and recording was controlled using custom software on an Apple Macintosh G4 computer via a MOTU 828 Mk II firewire I/O device (24 bit/44 100 Hz). The stimulus tones were passed through a Behringer 8000 ProXL headphone amplifier and presented to the subjects' ear canals via MB Quartz HB13.x transducers. The output of the transducers was coupled to the ear canal through the probe assembly of an Etymotic Research ER10B microphone. The output of the microphone and its preamplifier was passed through a Stanford Research SR560 low-noise voltage amplifier with band pass filtering between 0.3 and 20 kHz. The amplified output from the SR560 was digitized by the MOTU and stored on disk.

DPOAE recordings were made between f_2 frequencies of ~782 Hz ($2f_1-f_2=500$ Hz) and ~18 700 Hz ($2f_1-f_2=12\,000$ Hz) using stimulus levels of 65 (L_1) and 55 (L_2) dB SPL and a stimulus frequency ratio of (f_2/f_1) 1.22. In the analyses presented here, DPOAE data for f_2 frequencies between 1000 and 4000 Hz are presented to maintain consistency with the newborn group. In this frequency range, the stimulus tones were swept at a rate of 8 s/octave. Four to six such sweeps were averaged and DPOAE level, phase, and noise floor estimates were made using a least-square-fit algorithm (Long *et al.*, 2004). This analysis yielded DPOAE level, noise floor, and phase estimates at every 2 Hz around $f_2=1000$ Hz and every 6 Hz around $f_2=4000$ Hz. The stimulus levels were calibrated and system distortion measured in a B&K 4157 ear simulator using a B&K 4134 microphone. System distortion was approximately −35 dB SPL for the stimulus levels used in these recordings.

C. Characterization of fine structure

Data from both age groups were processed identically to estimate fine structure parameters of depth and spacing. Although the data from the two age groups were recorded using different frequency resolutions, even the lower resolution (11.7 Hz used in the infants) would have been sufficient to accurately characterize the DPOAE fine structure spacing reported from adult ears in the literature. The median value for every three successive data points was computed for DPOAE level and noise floor. Data points where the SNR between the level and noise-floor medians did not meet the criterion value of 6 dB were eliminated. Comparing the SNR of medians rather than single data points allowed the retention of fine structure minima where the local SNR was unfavorable.

Fine structure maxima and minima were identified based on the first and second derivatives of the DPOAE level function and the relationship between them. Data points where the first derivative was equal to zero were identified as extrema (maximum or minimum), and then further classified as a maximum or minimum based on the second derivative being negative or positive, respectively. Data points where the second derivative was equal to zero were marked as inflection points (Dhar *et al.*, 2002). Fine-structure depth for each period was computed as: $FS_{depth}=20\log_{10}(P_{max}/P_{avg(min)})$, where P_{max} is the DPOAE amplitude at a maximum and $P_{avg(min)}$ is the average DPOAE amplitude of the preceding and following minima. The frequency spacing of fine structure was computed as the ratio $f/\Delta f$, where f is the geometric mean between two adjacent minima and Δf is the frequency separation between them (Shera, 2003). The analysis

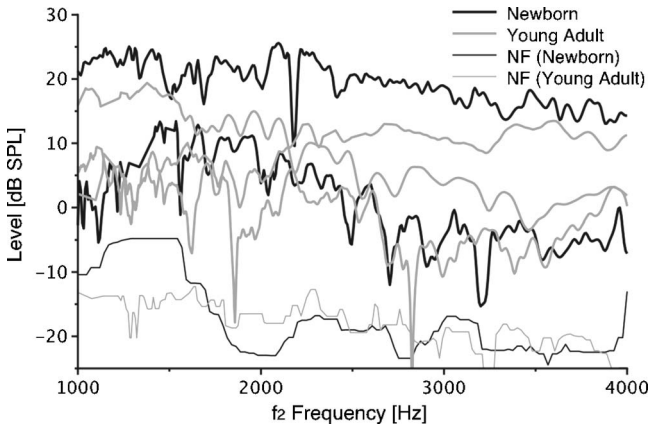

FIG. 1. DPOAE level from *two* newborn and *three* adult subjects in black and gray lines, respectively. Averaged noise floors for each group are presented using thinner lines in the same color. These subjects from each group were selected to represent the general limits of DPOAE level in each group.

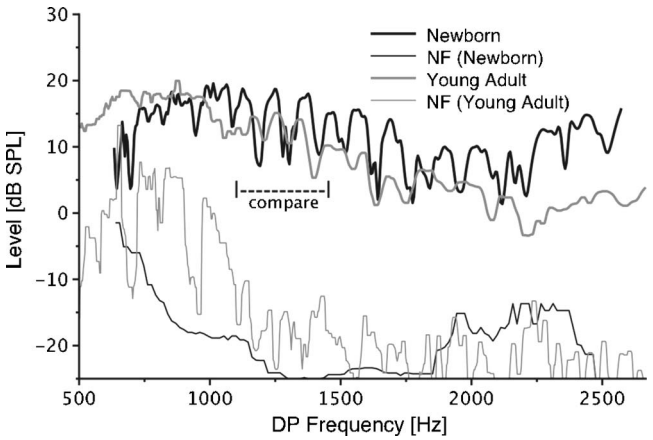

FIG. 2. Comparison of DPOAE fine structure in one member from each age group. These two subjects were chosen to represent examples of "deep" fine structure from each group. The frequency range marked by the horizontal dashed line allows direct comparison of approximately three fine structure periods in the two subjects. The noise floor from each subject is also displayed.

described previously was duplicated for DPOAE group delay (negative of the slope of phase). Only fine structure periods where depth was greater than 3 dB were included in further analyses, unless matching periods could be observed in the level and group delay data. Only 3 out of a total of 162 qualified fine structure periods were less than 3 dB deep. Further, to be included in the analyses, an odd number of inflection points had to be observed between a maximum and a minimum. Each fine structure period was classified as "log-sine" or "non-log-sine" based on the number of inflection points observed in each half period (see Dhar *et al.*, 2002, for details).

DPOAE level as well as fine structure prevalence, depth and spacing were compared across age groups, frequency, and gender in independent multiway analyses of variance (ANOVAs) using the statistical computing package R (R-Development-Core-Team, 2006). For analysis and display related to overall DPOAE level, f_2 frequency was used. Frequency was transposed to $2f_1-f_2$ for all fine structure related analyses and display. All dependent variables were assumed to be normally distributed and averaged across a range of frequencies to yield four values for nominal test frequencies—then treated as a repeated measure in the analyses. The frequency range over which each dependant variable was averaged is specified in the following section.

III. RESULTS

DPOAE levels from two newborn and three young adult subjects along with averaged noise floors are displayed in Fig. 1. The black lines represent data from the newborns while the gray lines represent data from the young adults. These subjects were selected from each age group to demonstrate the range of DPOAE levels observed. DPOAE levels recorded from one of the newborns are considerably higher across the entire frequency range, even if data from two young adults are combined for comparison in low (<2 kHz) and high (>2 kHz) frequency ranges. The lower limit of the range of DPOAE levels appears to be equivalent between the two age groups.

DPOAE levels as a function of frequency from one subject in each age group are displayed in Fig. 2 along with the corresponding noise floors. These subjects were chosen based on the presence of pronounced fine structure. Distinct fine structure periods are observed across the entire $(2f_1-f_2)$ frequency range for the newborn. In the young adult, such distinct fine structure is observed only between the frequencies of 1000 and 1500 Hz (marked in Fig. 2 for easy comparison). In this frequency range, the fine structure appears to be deeper in the newborn. Note that the general DPOAE level is equivalent in these two subjects across the entire frequency range.

Figure 3 allows comparison of mean DPOAE levels across age groups and sex. Three different estimates of DPOAE level are displayed for the newborns along with the noise floor in panel A. The solid circles represent the DPOAE level measured at the exact f_2 frequency in ten newborns. The gray circles represent DPOAE levels averaged over a span of 1000 Hz centered at each f_2 frequency in each newborn and then averaged across subjects. The frequency limits of recorded data in effect cause the averages to be over 500 Hz for the f_2 frequencies of 1000 and 4000 Hz. The open circles represent averages computed over a distance of 2 mm on the basilar membrane (Greenwood, 1990) centered around the nominal test frequencies in each subject and then averaged across subjects. The solid squares represent the average noise floor computed over a span of 2 mm also and the error bars represent ±1 standard deviation. The mean DPOAE levels following the 1000 Hz and 2 mm averaging are dissimilar at 1000 Hz but increasingly similar with increasing frequency. The same frequency range spans a greater distance on the basilar membrane with decreasing frequency. Thus, averages taken over a fixed frequency range in different regions of the cochlea are not equivalent. We choose to use the DPOAE levels averaged over a fixed distance on the basilar membrane (2 mm) for all further comparisons. In doing so we assume that Greenwood's map is valid in the infants, i.e., the length of the infant cochlea is

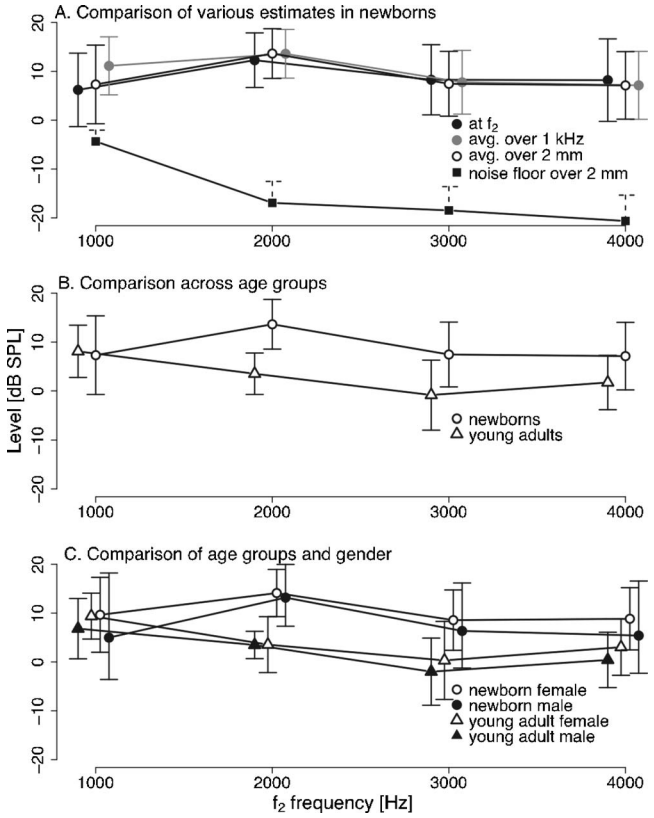

FIG. 3. Comparisons of various estimates of DPOAE levels as a function of f_2 frequency. Error bars represent ±1 standard deviation. (A) Comparison of average DPOAE level estimated using three different methods in ten newborns along with an estimate of the average noise floor (see the text). (B) Average DPOAE levels for ten newborns and ten young adults as a function of frequency. (C) Average DPOAE levels for each age group separated by sex. Symbols are "jittered" around the nominal frequency points on the abscissa to enhance visual clarity.

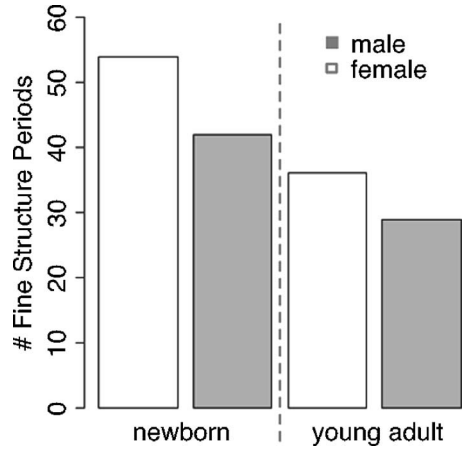

FIG. 4. Total number of fine structure periods observed in all (left) ten newborns and (right) ten young adults. Data from female and male subjects are presented in open and shaded bars, respectively. The main effect of sex was statistically significant (see Table I).

adult like. Using averages across fixed distances equalizes, to some extent, the number of data points representing different portions of the cochlea.

In panel B of Fig. 3, averaged DPOAE levels are compared across age group. Mean DPOAE levels are higher in the newborns at all frequencies except 1000 Hz. Overall, the grand average of DPOAE level was higher in the newborns by approximately 7 dB. The main effects of age group and frequency on DPOAE level were found to be statistically significant (see Table I). The data are further divided by sex in panel C of Fig. 3. In both age groups, there is a trend toward higher DPOAE levels in females even though no main effect of sex was observed in the analysis of variance. This sex difference is the smallest at 2 kHz in both age groups.

A count of qualified fine structure periods observed in male and female subjects belonging to the two age groups is displayed in Fig. 4. Female newborns had the largest number of fine structure periods followed by newborn males, young adult females, and young adult males. The main effect for age group was statistically significant as was the interaction between sex and age group (see Table I). The difference in the total number of fine structure periods observed was greater between male and female ears in the newborns.

Fine structure depth was significantly greater in newborns than young adults (Fig. 5 and Table I). Fewer fine structure periods were observed at $2f_1-f_2$ frequencies below 1000 Hz, primarily due to higher noise floors at these frequencies. Female ears showed significantly deeper fine structure in both age groups (Table I and Fig. 6). Figure 6 shows the distribution of fine structure depth in both age groups separated by sex. In newborn ears, the distributions in female and male ears show peaks between 4 and 8 dB, with a gradual decline beyond the peak. In contrast, the peak of the distribution in adults is between 2 and 6 dB and the decline in the distributions is more drastic beyond the maximum for young adults. Notably, no fine structure periods were observed in one young adult ear.

TABLE I. Results of multiway ANOVA with age group, sex, and frequency as the independent variables and either DPOAE level, fine structure prevalence, depth, or fine structure spacing as the dependent variables. Interactions between age group and frequency as well as between sex and frequency were not statistically significant for any dependent variable. To arrive at the mean DPOAE level estimates, a minimum of 20 data points (around 1 kHz) and a maximum of 85 data points (around 4 kHz) were averaged. The number of data points used in the analyses involving fine structure parameters at any frequency depended on prevalence and are shown in Figs. 4–8.

Variables	DPOAE Level	Fine structure prevalence	Fine structure depth	Fine structure spacing
Age Group	$p<0.01$, $F=15.34$	$p<0.01$, $F=26.62$	$p<0.01$, $F=31.67$	$p<0.01$, $F=34.77$
Sex			$p<0.05$, $F=5.4$	
Frequency	$p<0.05$, $F=5.29$			$p<0.01$, $F=70.26$
Age Group×Sex		$p<0.01$, $F=61.34$		
Age Group×Sex×Frequency				$p<0.01$,$F=16.64$

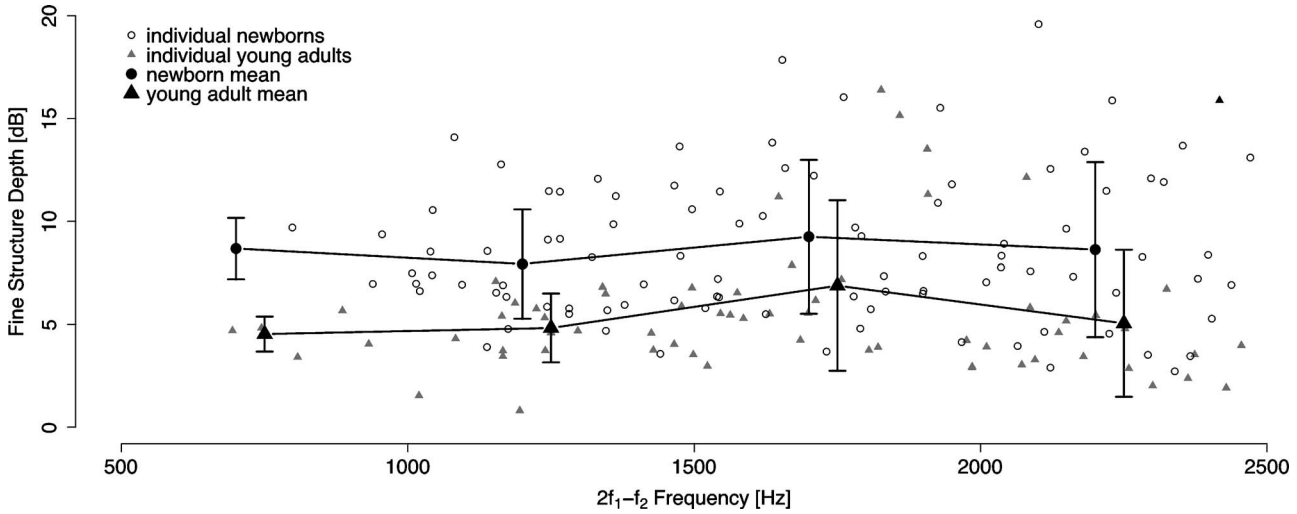

FIG. 5. Fine structure depth as a function of $2f_1-f_2$ frequency. Open circles and gray triangles represent individual data points from newborn and young adult subjects, respectively. Mean values of fine structure computed over 500 Hz ranges are displayed using the black circles and triangles for the newborns and young adults, respectively. The symbols representing the mean values are jittered along the abscissa for visual clarity. The error bars represent ±1 standard deviation. The main effect of age group was statistically significant (see Table I for details).

Spacing, computed as $f/\Delta f$, in newborns and young adults along with averages computed over 500 Hz ranges are presented in Fig. 7. A higher value of $f/\Delta f$ at any given frequency represents narrower fine structure spacing. Overall, fine structure was significantly narrower in young adults than newborns with a significant effect of frequency (Table I). A significant interaction between age, sex, and frequency was also observed. Distribution of fine structure spacing in the two age groups separated by sex is presented in Fig. 8. Note the clustering around $f/\Delta f=16$ in the young adults. Spacing in the newborn ears is more distributed at $f/\Delta f$ values less than 16.

The occurrence of log-sine and non-log-sine fine structure morphology in the two age groups separated by sex is displayed in Fig. 9. Examples of different types of patterns are presented in the top half of Fig. 9. White portions of the bars in the bottom half of the figure represent the number of log-sine fine structure periods observed, with the gray portions representing the number of non-log-sine periods. Fine structure periods were overwhelmingly non-log-sine in the newborns with 1 period of log-sine fine structure observed in male and female newborn ears each. In contrast, the majority of fine structure periods in the young adults were of the log-sine variety.

IV. DISCUSSION

Briefly, our results demonstrate significantly greater DPOAE levels ($p<0.01$) in newborns compared to young

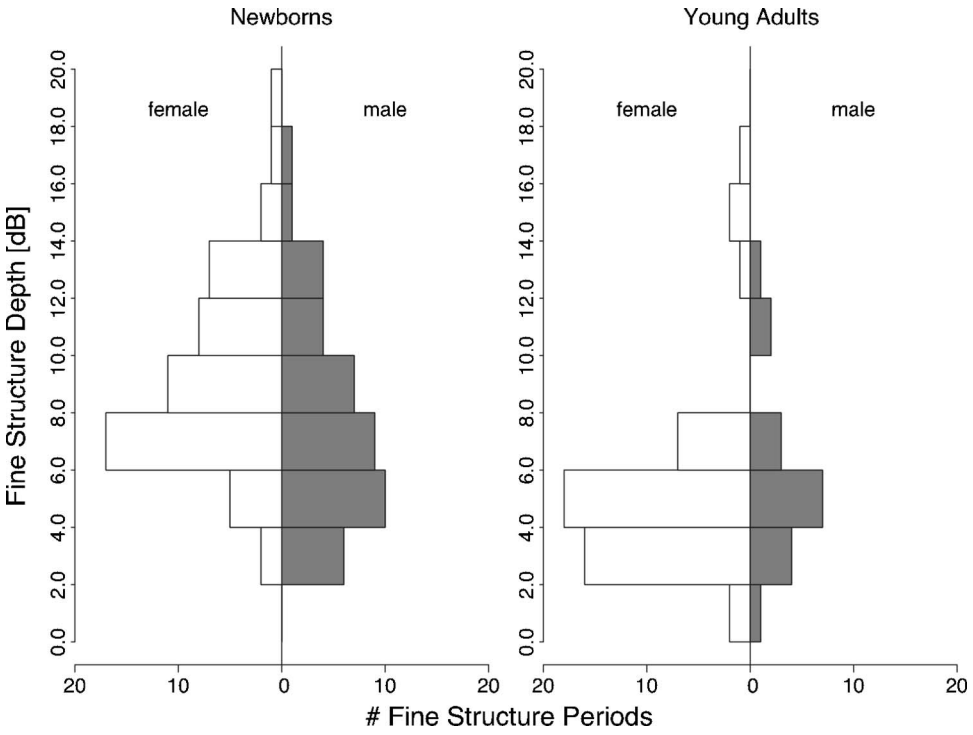

FIG. 6. Distribution of fine structure depth for the two age groups separated by sex. (Left) Data from the newborns with female and male subjects represented using open and gray bars, respectively. (Right) The format is repeated for the young adult subjects. Fine structure periods are grouped in 2 dB bins based on the measured depth. The main effect of sex was statistically significant (see Table I for details).

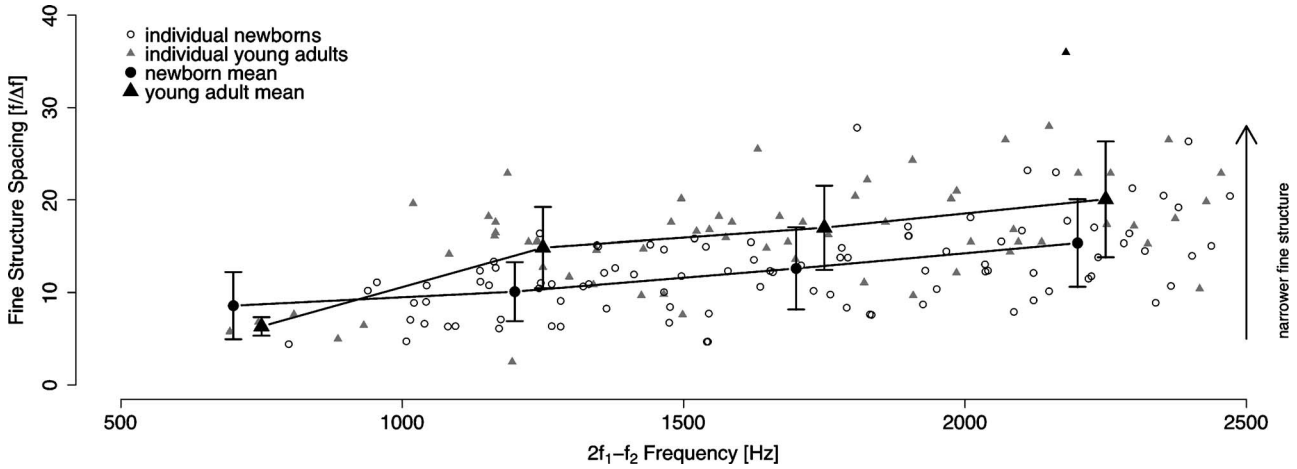

FIG. 7. Fine structure spacing computed as $f/\Delta f$ (see the text for explanation) as a function of $2f_1-f_2$ frequency. The format is identical to that of Fig. 5. Larger numbers along the ordinate represent narrower fine structure periods. The main effect of age group was statistically significant (see Table I for details).

adults, in agreement with previous results. We also report fine structure to be more prevalent, deeper, and spacing to be wider in newborns ($p<0.01$ in each case). Fine structure depth was greater in females of either age group ($p<0.01$). The distribution of $f/\Delta f$ was not clustered around any specific value and fine structure morphology was overwhelmingly non-log-sine in the newborns.

A. Cochlear maturation

Developmental timelines for the middle and inner ears of humans have, of necessity, commonly been obtained through indirect measures (e.g., Don *et al.*, 1993; Abdala, 1996; Keefe and Abdala, 2007). In contrast, more direct measures can be applied to laboratory animals in the study of developmental patterns and an advantage can be gained by informed application of these findings to humans. The gerbil is one of the most extensively studied species with regards to both anatomical and physiological development of the peripheral auditory system (Harris and Dallos, 1984; McGuirt *et al.*, 1995; Mills and Rubel, 1996; Overstreet and Ruggero, 2002; Overstreet *et al.*, 2002; Mills, 2004).

The developmental status of cochlear potentials (Harris and Dallos, 1984; Yancey and Dallos, 1985; McGuirt *et al.*, 1995), basilar membrane motion (Overstreet *et al.*, 2002), cochlear amplifier gain as measured by DPOAEs (Mills and Rubel, 1994, 1996), the neural response measured at the spi-

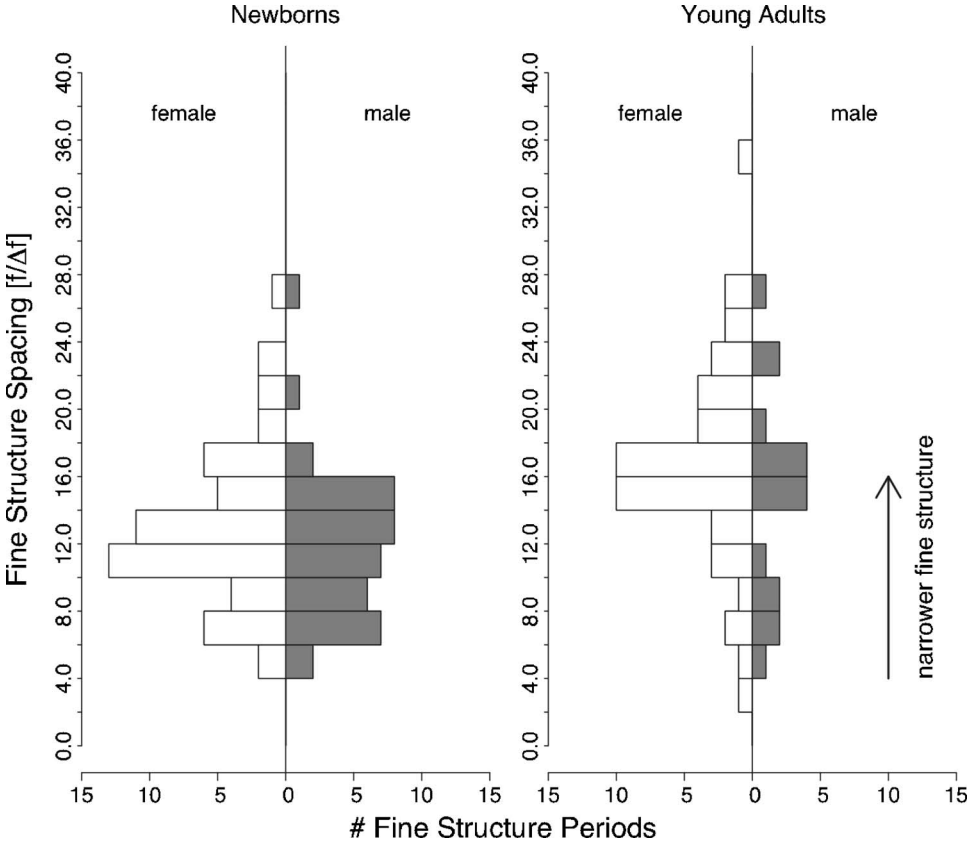

FIG. 8. Distribution of fine structure spacing in each age group and sex. The format is identical to that of Fig. 6.

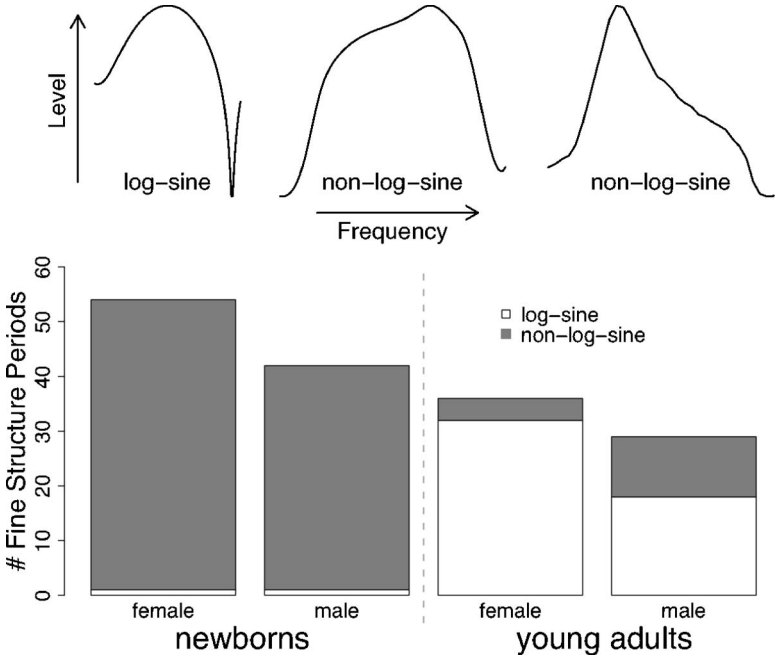

FIG. 9. Prevalence of log-sine and non-log-sine fine structure periods in each age group and sex. (Top) Examples of each type of fine structure period. (Bottom) The bars represent the total number of fine structure periods observed in each age group divided by sex. The white and gray portions within each bar represents the number of log-sine and non-log-sine periods observed in each group, respectively.

ral ganglion (Echteler *et al.*, 1989) and the auditory evoked potentials of the brain stem (Smith and Kraus, 1987) have been examined in the gerbil. The distinct advantage of many of these observations is that the developmental aspects of the cochlea can be studied independently of the concurrently maturing outer and middle ear system provided the appropriate experimental considerations are made (Harris and Dallos, 1984). On the other hand, the limitation of a vast majority of these observations is the place specific nature inherent in the experimental methodology, i.e., most of these measurements are made at the more accessible basal end of the cochlea and hence conclusions can only be drawn about the developmental status of the high-frequency end of the cochlea.

In the gerbil, the cochlear microphonic at the mid-basal turn of the cochlea is adult-like by 30 days after birth (dab) (Harris and Dallos, 1984) but the summating potential (Yancey and Dallos, 1985) and the endocochlear potential are not (McGuirt *et al.*, 1995). Even more basal in the cochlea (1.2 mm from the base; CF=34–37 kHz), the magnitude of basilar membrane vibration at 20 dab is similar to the postmortem adult (Overstreet *et al.*, 2002). However, the phase response of the basilar membrane response lags in development and is shallower than the adult post-mortem response, showing a total phase accumulation of 0.5 octaves compared to the 1.5 octave total accumulation seen in the post-mortem adult. This limited phase accumulation in the neonate gerbil is consistent with the lack of an adult-like traveling wave and suggests residual immaturities in the physical properties of the basilar membrane.

Cochlear amplifier function, as measured by the DPOAE I/O function, is not mature in gerbils across the entire frequency range until approximately 30 dab (Mills and Rubel, 1996). Mills and Rubel have hypothesized that these changes in cochlear function with age are driven by passive changes in basilar membrane mechanics, rather than maturation of cochlear amplifier function. Consistent with this hypothesis, they describe a shift in the passive cut off frequency, i.e., the highest frequency at which the basilar membrane can sustain a traveling wave, by approximately two octaves between 14 dab and adulthood. Neural tuning curves recorded from spiral ganglion cells in the midbasal turn of the cochlea appear to be adult like 17 dab (Echteler *et al.*, 1989). The auditory brainstem response (ABR) is first recordable in gerbils at 14 dab but shows continuing changes in latency and amplitude through 40 dab when it becomes fully adult-like (Smith and Kraus, 1987).

In summary, although some aspects of cochlear mechanics and biochemistry appear to be adult-like in the 30-day old gerbil, others, such as the phase response of the basilar membrane and the endocochlear potential are still maturing, albeit at a slower pace compared to the weeks of rapid development preceding this time period. Thus, although the active processes in the cochlea may be mature by 30 dab, immaturity of essential "substrates," such as the correct phase response of the *passive* basilar membrane mechanics, may be preventing the entire system from attaining adult-like functionality (see Overstreet *et al.*, 2002).

The gerbil cochlea around 30 dab may be a valid analog to the human infant around the time of birth. The gerbil has a 25 day gestational period and an onset of hearing at 14 dab (Smith and Kraus, 1987). At 30 dab, (55 days postconceptional age), the gerbil has been hearing for 16 out of 55 days, or 29% of its postconceptional existence. Similarly, a human infant around birth (38–40 weeks), with an onset of hearing at 28 weeks (Krumholz *et al.*, 1985), has been hearing for 10–12 out of 38–40 weeks, or 28% of the postconceptional period. Morey and Carlile (1990) used the period between conception and onset of hearing (the "silent period") in mammals as a foundation to equate the developmental timetables of various species. The gerbil at 30 dab (55 days postconceptional age) and the term-born human [40 weeks postconceptional age (PCA)] are at 141% and 142% of their silent periods, respectively. Thus, both of these approaches suggest that 30 dab in gerbils may be a rough analog to term

(38–40 weeks PCA) in human. Given what is known about gerbil cochlear function at 30 dab, it is possible that outstanding immaturities in physical properties of the basilar membrane could impede adult-like passive vibration along the entire basilar membrane of the human infant around the time of birth.

Similar to the immaturities observed in gerbil, significant OAE immaturities have been consistently observed in human newborns (see Abdala and Keefe, 2006, for a recent summary). The difference in DPOAE level between newborns and young adults (~7 dB) observed in this data set is consistent with reports in the literature (Lafreniere *et al.*, 1991; Bonfils *et al.*, 1992; Lasky *et al.*, 1992; Smurzynski *et al.*, 1993; Abdala, 1996). A significant portion of this difference has recently been attributed to immaturities in the outer and middle ears in the newborn human (Abdala and Keefe, 2006; Keefe and Abdala, 2007). However, discrepancies remain between DPOAE STCs of adults and 6-month old infants, when the middle ear transmission characteristics are predicted to approximate adult-like values (Abdala and Keefe, 2006). Thus, the possibility of residual immaturities in the human infant cochlea cannot be ruled out.

B. DPOAE components

The DPOAE level (L_{dp}) averaged across frequency and several subjects approximates the level of the component from the overlap region (L_{ovlp}) (Brown *et al.*, 1996; Shaffer and Dhar, 2006). Thus the larger L_{dp} in infants is directly related to a larger L_{ovlp}. Fine structure depth, on the other hand, is related directly to the level of the component from the DP CF region (L_{cf}), as evidenced by the disappearance of fine structure upon placing the DP CF region in an audiometric notch (Mauermann *et al.*, 1999b). Therefore the observation in the present study, of greater prevalence of fine structure and greater fine structure depth is linked to a larger L_{cf} in the newborns, as compared to the young adults. Further, assuming the relationship in magnitude between the two components is the same between newborns and adults, fine structure depth will be twice the magnitude of the CF component. This is explained by the fact that to the first order of approximation, fine structure depth is essentially the difference between the in-phase and out-of-phase combinations of the two DPOAE components. In our data, fine structure depth in newborns is greater than adult fine structure by approximately 3 dB, which would translate to an L_{cf} component that is larger by approximately 1.5 dB in this age group.

The observation of a larger L_{ovlp} in the newborns could conceivably be attributed entirely to immaturities in the outer/middle ear system rather than the cochlea. Specifically, a combination of stimulus levels that have been attenuated by an immature middle ear system and a boost to the returning DPOAE energy (due to smaller ear canal area) could account for the higher L_{ovlp} observed. Similarly, lower stimulus levels could also be responsible for a higher L_{cf} in the newborns (Konrad-Martin *et al.*, 2001). However, our data indicate L_{ovlp} is greater in infants than adults by 7 dB whereas L_{cf} is greater by a comparatively smaller amount (as calculated earlier). Given that the overlap and the CF components are at the same frequency ($2f_1-f_2$), they should be affected similarly during reverse transmission through the outer and middle ear systems. This suggests that the observed difference in the relative magnitudes of each component in infants versus adults is cochlear in origin. Said another way, bereft of any age-related difference in the generation mechanism of the CF component between newborns and adults, we would expect L_{cf} and L_{ovlp} to be larger by the same amount in the newborns or possibly, the age-related difference to be *greater* for L_{cf}, given the lower effective stimulus levels reaching the newborn cochlea.

Females, whether newborn or young adult, showed larger L_{dp} as well as deeper and more prevalent fine structure. In general, these differences between the two sexes were more apparent in the newborns. Differences in the transmission of sound through the outer and middle ears of the two sexes have been demonstrated in infants (Keefe *et al.*, 2000) and can, at least partially, explain these differences. Male infants showed a trend toward larger reflectance and equivalent volumes than female infants at low frequencies. At frequencies >4 kHz, conductance was also higher in males. These male–female differences, although subtle, suggest anatomical differences in the outer/middle ear structures between sexes even in the newborn period. Other work has suggested sex differences in cochlear physiology, as observed through features of the ABR (Don *et al.*, 1993; Sininger *et al.*, 1998) and OAEs (Burns *et al.*, 1992; McFadden, 1993; McFadden and Mishra, 1993; Bowman *et al.*, 2000). Consistent with anatomical data (Sato *et al.*, 1991), Don and Colleagues (1993) estimated a 13% difference in the length of the cochlea between males and females (males> females) using ABR measures. However, more recent data have shown this to be a gross overestimate, with the measured difference from a relatively large pool of temporal bones showing no significant difference in cochlear length between the sexes (Miller, 2007). Whether all or part of the male–female differences observed in our data are due to differences in transmission characteristics of the outer/middle ear can only be determined through careful juxtaposition of OAE and middle ear function measurements made over wide frequency ranges, an important direction for the future.

An immature middle ear in the infant could very well explain one other striking finding in our data set, the overwhelming prevalence of non-log-sine fine structure patterns. At least one way to arrive at these non-log-sine patterns of fine structure is to "mix" multiple iterations of the DPOAE energy, each additional component arriving in the ear canal with an increasing delay. The reader is directed to Dhar *et al.* (2002) for a detailed theoretical treatment of this phenomenon. Briefly, the impedance mismatch at the boundary between the cochlea and the middle ear acts as a barrier to return a portion of the outgoing DPOAE energy back into the cochlea. This returned energy then essentially becomes the stimulus tone in creating a stimulus frequency OAE generated at the CF region of $2f_1-f_2$. The stimulus frequency OAE (or a portion of it) is in turn returned to the ear canal as a part of the measured DPOAE package. Repeated occurrences of this sequence can lead to the observed non-log-sine patterns of fine structure.

These multiple iterations are relatively rare in the human adult, especially using moderate levels and stimulus frequency ratios around 1.2. When seen in adults, they are often observed at wide stimulus frequency ratios (~1.3) and low stimulus levels (~45 dB SPL), indicating increased involvement of the CF region. In the newborn however, the boundary condition at the junction of the cochlea and the middle ear is "exaggerated" due to the immaturities in the middle ear system. This would result in an increased proportion of energy being returned to the cochlea leading to multiple iterations and non-log-sine fine structure. The lowered stimulus levels at the infant cochlea (due to immature middle ear attenuation during forward transmission) may also contribute to the generation of these patterns.

Finally, the unexpected finding of broader fine structure in infants is intriguing. To the best of our knowledge three attempts, similar in many fundamentals, have been made to understand the phenomenon of fine structure in different types of OAEs (Kemp, 1979b; Zwicker and Schloth, 1984; Shera, 2003) and the relationship between OAE and hearing-threshold fine structure (Zwicker and Schloth, 1984). A relationship between the fine structures of DPOAEs, spontaneous OAEs, and estimates of loudness has also been demonstrated (Mauermann *et al.*, 2004). Although, an extended discourse about the intricacies of the previous approaches to fine structure spacing is beyond our scope, we apply the common elements in these models to our own observations. At the very basic level all three models are built on the idea of standing waves or interference patterns between the base and certain points (or regions) along the length of the cochlea. The locations of these regions of resonance along the length of the cochlea are determined primarily by the phase properties of the basilar membrane response and in turn are heavily dependent on the input impedance to the cochlea. In a simplistic view of these models then, fine structure would be more widely spaced if the phase gradient were shallower in infants compared to adults, consistent with the observations of Overstreet *et al.* (2002) in infant gerbils. The middle ear plays an important role in all these models and this role is addressed directly by two of the three authors (Kemp, 1979a, b; Shera, 2003). A change in the input impedance to the cochlea induced by a change in the middle ear would induce a shift in fine structure pattern. However, this shift is predicted to alter the entire pattern of fine structure in frequency, without significantly affecting the spacing between adjacent maxima in DPOAE level (Kemp, 1979a, b; Shera, 2003). Thus, the wider fine structure in infants is not easily explained by immaturities in the conductive pathway and may be suggestive of residual cochlear immaturities in the human newborn, possibly related to passive basilar membrane motion.

The peak of the distribution of fine structure spacing ($f/\Delta f$) in adults is around 16, in agreement with reported spacing of spontaneous OAEs (Shera, 2003) as well as spacing of DPOAE fine structure (Long *et al.*, 1999). In contrast, the distribution of spacing is more dispersed and does not show a clear peak in newborns. This scatter may be indicative of a dynamic system going through maturational change at slightly different rates for each individual infant subject.

In closing, we have demonstrated several differences between DPOAE fine structure in human newborns and young adults. Many of these differences can be explained based on differences in outer and middle ear anatomy and physiology between these age groups. However, we also have demonstrated a striking difference in fine structure spacing between these age groups that may be suggestive of residual cochlear immaturities in the term born human. In particular, differences in fine structure spacing between newborns and adults would be consistent with observed immaturities in passive basilar membrane motion in gerbils, which are the last to mature; well after active cochlear processes have attained adult-like function.

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