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Effect of age on click-evoked otoacoustic emission

A systematic review☆

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Abstract

OBJECTIVE: The aims of this study were to investigate the changes of the total intensity of transient evoked otoacoustic emission (TEOAE) and signal-to-noise ratio in various frequency bands as a function of aging, and to explore the role of age-related decline of cochlear outer hair cells.

DATA SOURCES: The literature was searched using the PubMed database using 'transient-evoked otoacoustic emissions' as a keyword. Articles were limited as follows: Species was 'Humans'; languages were 'English and Chinese'; publication date between 1990-01-01 and 2010-12-31. The references of the found were also searched to obtain additional articles.

DATA SELECTION: Inclusion criteria: (1) Articles should involve the total TEOAE level or signal-to-noise ratio. (2) The measurement and analysis system used was Otodynamics ILO analysis system (ILO88, ILO92, ILO96 or ILO292). (3) Studies involved groups of greater than 10 subjects and TEOAE results were from normally hearing ears. (4) If more papers from the same author or laboratory analyzed the same subjects, only one was used.

MAIN OUTCOME MEASURES: The correlations of the age scale with the total level and signal-to-noise ratio of TEOAE was determined, respectively.

RESULTS: (1) TEOAE total level gradually increased until 2 months of age, and then decreased with increasing age. Significant negative correlations between total TEOAE level and age were found (r = −0.885, P = 0.000). (2) The most rapid decrease of TEOAE amplitude occurred at 1 year old. The total TEOAE level decreased about 4.25 dB SPL between 2 months to 1 year old, then about 0.26−0.52 dB SPL from 1 year to 10 years old, about 0.23 dB SPL from 11 years to 25 years old, and about 0.14 dB SPL from 26 years to 60 years old. (3) The signal-to-noise ratio in the frequency bands centered at 1.5, 2, 3 and 4 kHz decreased with increasing age after 2 months of age. Significant negative correlations between the signal-to-noise ratio and age were found for frequency bands ranging from 1.5 kHz to 4 kHz, with the highest correlations at 4 kHz (r = −0.890, P < 0.01), then at 3 kHz (r = −0.889, P < 0.01), at 2 kHz (r = −0.850, P < 0.01) and at 1.5 kHz (r = −0.705, P < 0.05). Conversely, a positive correlation between the signal-to-noise ratio centered at 1 kHz and age was found, but was not statistically significant (r = 0.298, P = 0.374).

CONCLUSION: The total TEOAE response level decreased with increasing age after the first 2 months of age. The signal-to-noise ratio also decreased with increasing age in frequency bands above 1.5 kHz. The signal-to-noise ratio in higher frequencies decreased faster than in lower frequencies, leading to the maximum signal-to-noise ratio shift form 3.2−4.0 kHz in neonates to 1.5 kHz in adults, and further decreasing the total TEOAE response level. The age-related TEOAE spectrum peak shift is most likely because the outer hair cells functioning in higher frequencies are more prone to damage than those for lower frequencies.

Key Words: age; transient-evoked otoacoustic emission; signal-to-noise ratio; outer hair cells; meta-analysis

Abbreviations: TEOAE, transient-evoked otoacoustic emission; SNR, signal-to-noise ratio; OHCs, outer hair cells; PTT: pure tone threshold

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INTRODUCTION

Transient-evoked otoacoustic emissions (TEOAE) are low-volume sounds that originate from the cochlea and are recorded in the external ear canal after brief acoustic stimuli such as clicks or tone bursts, which is an objective, rapid, accurate and non-invasive way to determine the function of outer hair cells (OHCs). It has been widely used in neonatal hearing screening and audiological diagnosis. As a research tool, TEOAE provide a non-invasive window on intracochlear processes and this has led to new insights into the mechanisms and function of the cochlea and also to a new understanding of the nature of sensory hearing impairment[1]. Advanced age can lead to ganglion cell loss, strial atrophy and stiffness of the basilar membrane, which leads to hearing loss. It can also lead to OHC degeneration or loss. Because otoacoustic emission testing is recognized as a sensitive and objective measure of cochlear OHC function[2-3], age may influence the results of TEOAE testing. TEOAE intensity has already been reported to be greater in neonates and children than in adults. Collet *et al* [4] showed that TEOAEs decrease with increasing age and that TEOAEs in elderly subjects are of relatively lower amplitude, with a spectrum shifted towards lower frequencies. Kon *et al* [5] investigated 275 subjects ranging in age from 1 month to 39 years. Their results showed that the decrease of TEOAE amplitude in the first 6 years of life is rapid. At later ages, the decrease of TEOAE amplitude continues more slowly[5].

Another report showed that TEOAE response levels in frequency bands between 2.4 kHz and 4 kHz were significantly higher in children aged less than 1 year than in older children and adults. Children aged 1–5 years had higher TEOAE levels in some of those bands than did teens and adults[6]. Shi *et al* [7] showed the response spectrum shifted between newborns and young adults, further implying that TEOAE response decrease in adults is mainly due to response decline specifically in the higher frequencies.

In these previous studies, the subjects' age construction was different, and the age distributions in each group were wide[5-7]. The change of TEOAE amplitude with age was uneven. There remained a need for a meta-analysis to more clearly show how total intensity and signal to noise ratio (SNR) of TEOAE changed with age.

DATA AND METHODS

Data retrieval

PubMed was searched using 'transient-evoked otoacoustic emissions' as a keyword. Publications were limited to: species 'Humans'; Languages 'English and Chinese'; publication date from 1990-01-01 to 2010-12-31. The references of these articles that related to TEOAE level or SNR of normal subjects were also searched and were included if the full text of the reference met the inclusion criteria.

Inclusion and exclusion criteria

A total of 168 articles were found by electronic literature search. Publications were included in accordance with the following conditions: (1) results involved TEOAE total strength or SNR, even these data were indirectly obtained. (2) The measurement and analysis system used was Otodynamics (London, UK) ILO analysis system (ILO88, ILO92, ILO96 or ILO292). (3) At least 10 subjects were included in each group. (4) If multiple papers from the same author or laboratory were found using the same subjects, only one was used. (5) All neonates and children were normal subjects, without family or personal history of deafness, and with available TEOAE recording. No such selection criteria were required for neonates and children in many previous articles[8-19]. For our review, a normal hearing ear was defined for adult subjects as having a hearing threshold better than 25 dB HL at frequencies between 250 Hz and 4 kHz, and normal 226 Hz or 220 Hz tympanometric parameters. The criteria for normal hearing varied across previous studies[20-30], but most researchers used stricter criteria than ours, especially for young adults[22-29]. Exclusion criteria for adults included: (1) middle ear pathology, (2) family history of hereditary hearing loss and (3) past exposure to noise or ototoxic drugs. Ultimately, 24 English papers and four Chinese papers were included and analyzed.

Quality evaluation and data extraction

The SNR data at 1, 1.5, 2, 3, and 4 kHz or 0.8, 1.6, 2.4, 3.2, and 4 kHz were collected for further statistical analysis. The mean TEOAE levels were also collected. To analyze the effect of age on TEOAE level, the subjects were divided into age categories. Because of the dramatic change in hearing during this period, the first category contained subjects from newborn to 1 month old. TEOAE levels also change greatly between 1 and 2 months, so this period was defined as the next category. The remaining categories were: 2 months to 1 year old, 1 to 5 years old and then in 5 year increments up to 60 years old.

In a report from Driscoll *et al* [19], the mean TEOAE level was calculated by averaging the TEOAE levels in the female right ear, female left ear, male right ear and male left ear in children with no history of auditory problems. In contrast, the mean TEOAE level in the studies from Pavlovcina *et al* [21] and Stenklev *et al* [27] was calculated using the formula: mean level of TEOAE or SNR = (mean of female level or SNR × female number + mean of male level or SNR × male number)/(female number + male number).

Main outcome measures

The correlation between age scales and total TEOAE level; The correlation between age scales and SNR in different frequency bands.

Statistical analysis

To determine the effect of age on TEOAE level and SNR, we analyzed the correlations between the age categories and total TEOAE levels and between age and SNR at five frequency bands using Spearman's correlation coefficient. The validity of Spearman's correlation coefficient was tested. The correlations were considered statistically significant when the *P* value was less than 0.05. All statistical analyses were performed with SPSS 13.0 software (SPSS, Chicago, IL, USA). Scattergrams were drawn by SPSS 13.0 and GraphPad Prism V5.0 (GraphPad Software, Inc., San Diego, CA, USA).

RESULTS

Data retrieval

A total of 168 studies were obtained from the initial search. After review of the title and abstract, 113 studies were excluded. Forty-three of these were excluded because they included abnormal subjects with middle ear pathology, tinnitus, hearing loss or other diseases (vestibular neuritis, auditory listening problems, rheumatoid arthritis, traumatic brain injury), patients following surgery (acoustic neuroma surgery, stapes surgery) or chemotherapy (vincristine, cisplatin or platinum-containing drugs). Thirty-four articles were excluded because the study used a different recording method or technique for measuring TEOAE. Ten articles were excluded because they primarily reported research of the effects of noise on the human cochlea. Seventeen articles were excluded because they focused on hearing screening programs and did not show data directly. Nine review articles and other irrelevant papers were excluded.

After reading the full text of the remaining articles, thirty-six articles were excluded. Eleven articles were excluded because data was not directly displayed and could not be calculated indirectly. Three articles were duplicated papers. Nine articles used other measurement and analysis systems and thirteen articles did not match our inclusion criteria. Nine additional articles that met the inclusion criteria were obtained from the references of the excluded articles and were included (Figure 1).

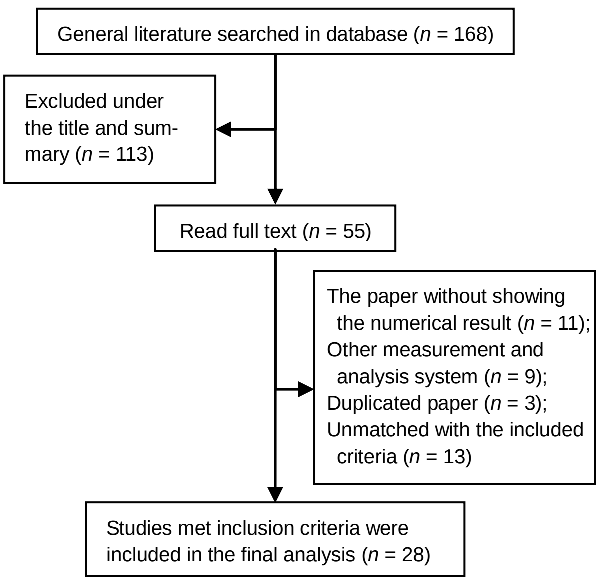

Figure 1 Flowchart of the included studies.

Total TEOAE levels changed with age

Figure 2 and Table 1 show that total TEOAE levels primarily increased in the first 2 months of life, and then decreased slowly with increasing age.

The total TEOAE level increased by approximately 2.55 dB SPL from birth to 2 months (over the first two age categories). At 2 months, the total TEOAE level began to decrease, and declined by 15.35 dB SPL by 60 years of age. This decrease occurred at approximately 0.26 dB SPL per year but was asymmetric or nonlinear. The most rapid decrease of TEOAE amplitude occurred in the first year of life. The total TEOAE level decreased about 4.25 dB SPL between age categories 2 and 3 (2 months to 1 year old).

Table 1 Entire transient evoked otoacoustic emission (TEOAE) level (dB SPL) in different age scales

Reference	Age	Age scale	Subject (ears)	TEOAE level
Mean				
Collet *et al* (1993)[4]	3.8 days	1	88(176)	15.20
Engdahl *et al* (1994)[8]	3.1 days	1	100(192)	20.10
Aidan *et al* (1997)[9]	2 days	1	582(1 152)	21.75
Paludetti *et al* (1999)[10]	3 days	1	320(524)	21.64
Mazlan *et al* (2007)[11]	61.7 hours	1	42(42)	21.40
Thornton *et al* (2003)[12]	1 day	1	17 526(28 398)	17.65
Saitoh *et al* (2006)[13]	4 days	1	157(314)	18.28
Berninger (2007)[14]	4 days	1	(60431)	18.80
Zhang *et al* (2008)[15]	2–7 days	1	1 033(2 066)	17.00
Prieve *et al* (2009)[16]	1.5 days	1	79(137)	18.65
Shi *et al* (2010)[7]	2.67 days	1	120(240)	15.18
Mean				18.70
Kei *et al* (1997)[17]	2 months	2	568(1 051)	19.25
Driscoll *et al* (1999)[18]	2 months	2	627(1 254)	21.11
Saitoh *et al* (2006)[13]	5.5 weeks	2	134(268)	19.06
Prieve *et al* (2009)[16]	4.6 weeks	2	79(137)	21.95
Mazlan *et al* (2007)[11]	6–7 weeks	2	42(42)	24.90
Mean				21.25
Engdahl *et al* (1994)[8]	3 months	3	33(55)	18.60
	6 months	3	30(44)	16.30
	12 months	3	28(39)	16.10
Mean				17.00
Kon *et al* (2000)[5]	1–3 years	4	(45)	15.80
	4–6 years	5	(76)	13.10
	7–9 years	5	(94)	13.10
Driscoll *et al* (2000)[19]	6.2 years	5	574(1 148)	14.80
Balatsouras *et al* (2006)[20]	9.1–9.5 years	5	66(132)	16.50
Mean				14.38
Kon *et al* (2000)[5]	13–15 years	6	(40)	12.40
	10–12 years	6	(63)	12.60
Pavlovcinova *et al* (2010)[21]	12.9 years	6	229(458)	13.29
Mean				12.76
Moulin *et al* (1993)[22]	21.25 years	8	135(270)	11.60
Vinck *et al* (1996)[23]	20–22 years	8	101(202)	10.60
Khalfa *et al* (1997)[24]	22.7 years	8	70(140)	9.50
Guo *et al* (1999)[25]	22.9 years	8	30(60)	10.27
Ferguson *et al* (2000)[26]	21.5 years	8	93(186)	10.38
Stenklev *et al* (2003)[27]	19–26 years	8	20(40)	11.30
Quaranta *et al* (2001)[28]	23.7 years	8	12(24)	7.60
Shahnaz (2008)[29]	23.7–24.5 years	8	81(160)	16.20
Mean				10.92
Shahnaz *et al* (2008)[29]	24.7–27.8 years	9	81(151)	14.10
Shi *et al* (2010)[7]	26.7 years	9	32(64)	9.51
Kei *et al* (2003)[30]	28.1–29.0 years	9	60(115)	8.90
Quaranta *et al* (2001)[28]	39.7 years	11	11(22)	7.90
Quaranta *et al* (2001)[28]	60 years	15	10(19)	5.90
Stenklev *et al* (2003)[27]	60–64 years	16	37	4.74
	65–69 years	17	38	6.03
Quaranta *et al* (2001)[28]	71 years	18	11(21)	5.40

The entire TEOAE level was increased primarily within the first 2 months of life, and then decreased slowly with increasing age up to older than 60 years old.

The age scale range was 5 years. Neonates corresponded to the first scale because of the great change during this short term; 1 month old to 2 months old corresponded to the second scale, since in this term the TEOAE level also varied greatly; 2 months old to 1 year old corresponded to the third scale. 1 year to 5 years old corresponded to the fourth scale. 5 years to 10 years old was the fifth scale.

Total TEOAE then decreased 2.62 dB SPL between age categories 3 and 5 (1 year to 10 years old), a decrease of 0.26–0.52 dB SPL per year. Between age categories 5 and 8 (11 years to 25 years old), total TEOAE decreased 3.46 dB SPL, or 0.23 dB SPL per year. The decrease from age category 8 to 15 (26 to greater than 60 years old) was 5.02 dB SPL, or 0.14 dB SPL per year. Significant negative correlations between total TEOAE level and age category were found using the Spearman correlation analysis (r = −0.885, P = 0.000). Total TEOAE level decreased with increasing age. The fitted value of curve fit (r^2 = 0.811) was higher than the fitted value in linear fit (r^2 = 0.783), so the relation between total TEOAE level and age category appeared to be curvilinear (Figure 2).

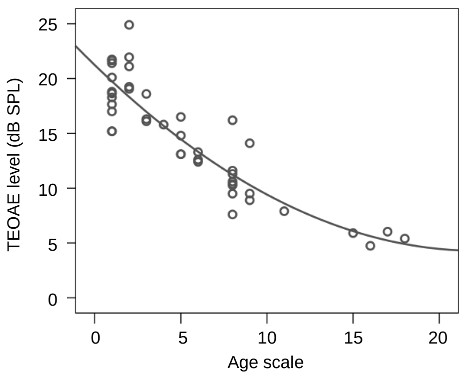

Figure 2 Scattergrams and correlation analysis between entire transient evoked otoacoustic emission (TEOAE) level and age scale.

Significant negative correlations between entire TEOAE level and age scale were found by Spearman correlation analysis (r = −0.885, P = 0.000).

TEOAE SNR changed with age

To clearly show the frequency-dependent change in TEOAE level with age, the TEOAE level was analyzed in five frequency bands. The SNR in the same frequency bands reported in different studies showed a variety of results (Tables 2 and 3).

Table 2 Signal-to-noise ratio in frequency bands centered at 2.4, 3.2 and 4 kHz changed with increasing age

Source	Age	Signal-to-noise ratio		
		2.4 kHz	3.2 kHz	4 kHz
Shi *et al* (2010)[7]	2.6 days	14.70	16.90	15.71
Cassidy *et al* (2001)[31]	2 days	13.69	15.07	13.27
Kei *et al* (1997)[17]	2 months	13.25	15.08	15.17
Driscoll *et al* (1999)[18]	2 months	15.08	17.07	16.53
Driscoll *et al* (2000)[19]	6 years	15.71	16.40	15.53

Before 6 years old, the frequency band of maximum signal-to-noise-ratio was stably centered at 3.2 kHz or 4 kHz.

Across the studies, the frequency band of maximum SNR was stable in subjects within a similar age group but shifted with age. For neonates and infants, the maximum SNR was centered at 3.2 kHz or 4 kHz. For children, the maximum SNR was centered at 2 kHz. For adults, the maximum SNR decreased to 1.5 kHz (Figure 3). The first shift of the maximum SNR occurred between 6 and 9 years old. The second shift was between 9 and 12 years old. After 12 years old, the frequency band of maximum SNR was stably centered at 1.5 kHz.

Table 3 Signal-to-noise ratio in frequency bands centered at 1, 1.5, 2, 3 and 4 kHz changed with increasing age

Source	Age scale	Age	Signal-to-noise ratio		
			1 kHz	1.5 kHz	2 kHz
Zhang *et al* (2008)[15]	1	2–7 days	−1.88	8.80	14.09
Mazlan *et al* (2007)[11]	1	61.7 hours	6.30	14.80	18.50
Saitoh *et al* (2006)[13]	2	5.5 weeks	4.58	12.81	17.33
Mazlan *et al* (2007)[11]	2	6–7 weeks	7.10	18.00	22.10
Balatsouras *et al* (2006)[20]	5	9.3 years	4.30	11.43	18.14
Pavlovcinova *et al* (2010)[21]	6	12.9 years	2.23	7.220	5.60
Shahnaz (2008)[29]	8	24 years	7.00	10.00	7.90
Keppler *et al* (2010)[32]	8	24.2 years	8.81	10.55	8.99
Shahnaz (2008)[29]	9	26.4 years	5.70	8.20	5.10
Shi *et al* (2010)[7]	9	26.7 years	6.79	9.81	8.48
Keppler *et al* (2010)[32]	12	40.4 years	3.70	4.49	3.66
r			0.298	−0.705	−0.850
P			0.374	0.015	0.001

Source	Age scale	Age	Signal-to-noise ratio	
			3 kHz	4 kHz
Zhang *et al* (2008)[15]	1	2–7 days	16.93	15.69
Mazlan *et al* (2007)[11]	1	61.7 hours	20.10	21.50
Saitoh *et al* (2006)[13]	2	5.5 weeks	19.14	17.81
Mazlan *et al* (2007)[11]	2	6–7 weeks	24.20	13.80
Balatsouras *et al* (2006)[20]	5	9.3 years	16.86	17.13
Pavlovcinova *et al* (2010)[21]	6	12.9 years	5.99	2.96
Shahnaz (2008)[29]	8	24 years	6.50	4.50
Keppler *et al* (2010)[32]	8	24.2 years	7.41	6.18
Shahnaz (2008)[29]	9	26.4 years	4.60	1.90
Shi *et al* (2010)[7]	9	26.7 years	8.46	3.54
Keppler *et al* (2010)[32]	12	40.4 years	4.61	1.49
r			−0.889	−0.890
P			0.000	0.000

The age scale range was 5 years.

Neonates was the first scale because of the great change during this short term; 1 month to 2 months old was the second scale, since in this term the TEOAE level also varied greatly; 2 months to 1 year old was the third scale.

1 year to 5 years old was the fourth scale. 5 years to 10 years old was the fifth scale.

As shown in Table 3 and Figure 3, the SNR in each analyzed frequency band also tended to change with increasing age. The SNR in the frequency band centered at 1 kHz increased with increasing age from 2 months to young adults, and then decreased slowly with increasing age. The SNR in the frequency bands centered at 1.5, 2, 3 and 4 kHz decreased with increasing age consistently after 2 months old (Figure

4). Significant negative correlations between the SNR in each frequency band and age category were found for the frequency bands ranging from 1.5 kHz to 4 kHz, with the highest correlations at 4 kHz (r = −0.890, P < 0.01), then at 3 kHz (r = −0.889, P < 0.01), 2 kHz (r = −0.850, P < 0.01) and 1.5 kHz (r = −0.705, P < 0.05). A positive correlation between the SNR centered at 1 kHz and age was found, but was not statistically significant (r = 0.298, P < 0.374).

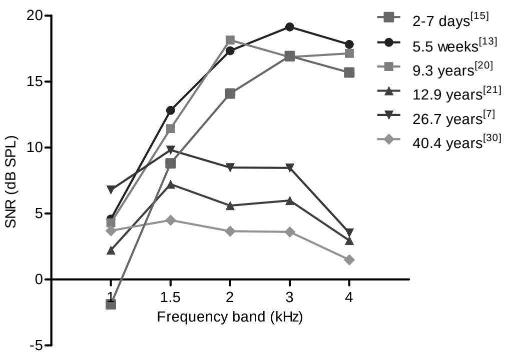

Figure 3 Frequency band of maximum signal-to-noise ratio (SNR) shifts with age. The maximum SNRs were centered at 3.2 kHz frequency band for neonates from 2 to 7 days after birth and infants at 5 weeks after birth.

The maximum SNRs were centered at 2 kHz frequency band for 9-year-old children. The maximum SNRs were centered at 1.5 kHz frequency band in 12-year-old children and adults.

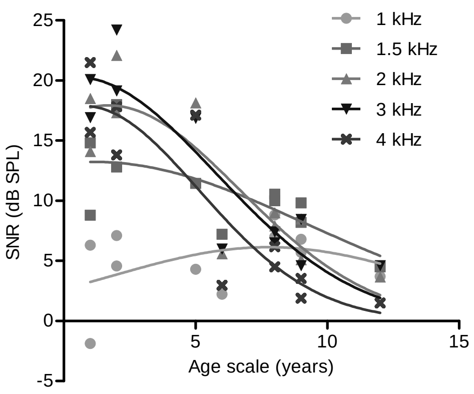

Figure 4 Scattergrams and curve of the relationship between signal-to-noise ratio (SNR) in frequency band and age scale.

The slope of curve in higher frequency band was steeper than that in lower frequency band.

CONCLUSION

TEOAE level increases in the first 2 months of age

A number of studies showed that the overall TEOAE level increased in the first 1 or 2 months of life[11, 16]. Clear age dependence exists in newborn emissions. It has been reported that the total TEOAE level increases distinctly as a function of age, up to 48 hours[12]. Subsequently, the TEOAE level increases more slowly up to the maximum at 2 months of age. The reason for the increase of TEOAE level in the first 2 months is not due to an increased amount of OHCs, as these do not proliferate after birth. Otoacoustic emission is produced by contraction of OHCs, which are largely innervated by the medial olivo-cochlear bundle. However, since medial olivo-cochlear bundle function is already mature at birth, development of the medial olivo-cochlear bundle also cannot account for the increase in TEOAE in the first 2 months of life[33]. In addition, the efferent medial olivo-cochlear bundle system represses OHC motility. The effect of a normal healthy medial olivo-cochlear bundle is to suppress TEOAE amplitude. It is inconsistent with the change of TEOAE amplitude in neonates.

The reason for the increasing TEOAE level in the first few days of life may be the reduction of middle ear effusion and ear canal debris. The low emission level recorded immediately after birth can be attributed to a transitory sound-conductive hearing loss due to residual amniotic fluid in the middle-ear cavity or to Eustachian tube dysfunction. Doyle *et al* [34] found a higher incidence of middle ear effusion (22.7%) in neonates 5 to 48 hours old (mean 25.7 hours). Of 200 infants, 66 (33%) had effusion in at least one ear, whereas 24 (12%) had bilateral effusion. Middle ear effusion will reduce emissions energy below approximately 2 kHz. Doyle *et al* [34] further showed that the middle ear effusion decreased with increasing age, which may be the reason for the TEOAE increase in the first few days of life. In addition, outer ear factors, such as ear canal debris, can affect TEOAEs. Ear canal debris in the neonatal period is composed primarily of vernix caseosa. Vernix has been found to at least partially obstruct the external ear canal in many neonates and then dissipates within a few days. However, Prieve *et al* [16] showed that the overall increase in TEOAE level was not related to changes in ear canal debris between birth and one month old.

Model predictions also indicate that greater forward power is transmitted through the ear canals and middle ears of infants aged 1.5 months than that of newborns[35]. Moreover, reverse power flow decreases with age. At 1 month after birth, reverse power transmittance is lower than at birth[35]. So, TEAOE increase during the newborn period may be because, by 1 month after birth, relatively more power from the click in the 3−4 kHz bands is transmitted to the cochlea through the ear canal and middle ear. At the same time, the ear canal area has not yet noticeably reduced the reverse ear canal power transfer[16].

TEOAE level decreases between 2 months and 6 years old

Table 1 shows that the total TEOAE level decreased with increasing age after 2 months old. Engdahl *et al* [8] showed that the median amplitude of TEOAEs was significantly reduced from 19.6 to 18.0 dB SPL between 3 days and 3 months of age. The primary decrease in TEOAE level likely occurs between 2 and 3 months of age. Moreover, the rate of this decrease was asymmetric or nonlinear. The greatest decrease of total TEOAE level occurred between 2 months old and age category 5 (5–10 years old), which was consistent with the results of Kon *et al* [5].

The morphology of the cochlea does not change after birth, as evidence suggests that the cochlea is mature at 40 weeks after conception[36]. Therefore, the decrease in TEOAE level between 2 months to 6 years old is not likely related to cochlear maturation.

Otoacoustic emission pressure in the outer ear canal depends on both ear canal and middle ear volume. The decrease of total TEOAE levels between 2 months and 4–6 years is more dependent on anatomical changes in the outer and middle ear, which may relate to volume and impedance characteristics[37]. Otoacoustic emission levels are higher in the small ear canal of infants than in that of children[38-39]. The external auditory canal is reported to elongate most rapidly from 6 to 12 months after birth, and then continues to increase in length until 6–7 years old[37]. These changes seem to correspond to the age-dependent changes in otoacoustic emissions observed in this analysis. The decrease in TEOAE level was most dramatic between 2 months and 1 year old, which is consistent with the findings of Kon *et al* [5].

The middle ear functions as a bidirectional connection between the cochlea and the eardrum. Just as a horn can be used either to enhance hearing or as a trumpet to strengthen the voice, the middle ear can work in reverse as a kind of stethoscope to record vibrational activity deep inside the cochlea[40]. The middle ear volume is smallest in neonates and increases with development. Model estimates of middle ear cavity volume are 454 mm^3 in infants and 640 mm^3 in adults[41]. Age-related change in middle ear cavity volume may also be related to the rapid decrease in TEOAE levels in the first 6 years of life.

TEOAE level decreases after 6 years old

Total TEOAE level reduction continued more slowly after 6 years old[5, 42]. Groh *et al* [42] divided 126 subjects between 6 and 25 years old into four age groups and showed that TEOAE response in the 16–20 year old groups and the 21–25 year old groups was significantly lower than in the 6–10 year old groups and the 11–15 year old groups. Norton and Widen[39] found that subjects aged 0.0–9.9, 10.0–19.9 and 20–29.9 years had significantly different click-evoked otoacoustic emission levels. Satoh *et al* [43] divided 173 subjects aged 15 years and over into three age groups, and also found TEOAE level reduction with increasing age. All of the above results are consistent with our analysis showing that TEOAE level reduced with increasing age after 6 years old. However, Uchi *et al* [44] did not find a statistically significant difference in TEOAE levels between subjects aged 31–50 years and those older than 50 years. Because the TEOAE level decreases very slowly after 20–25 years old, there was less difference in TEOAE levels between these older groups.

Most of the results consistently demonstrated that TEOAE amplitude tends to decrease with age. At the same time, the noise floor level was decreased significantly until 6 years old and then remained constant[5]. The external auditory canal is not significantly elongated after 6–7 years old[37]. This suggests that cochlear micromechanics deteriorate with increasing age in normal hearing ears[43-44]. Otoacoustic emission can reflect OHC motility. Age-related changes were predominantly determined by an otoacoustic emission generator system, *i.e.* at the level of the OHCs.

Reduction of distortion-product otoacoustic emission was relatively consistent with OHC loss. On average, 1% OHC loss results in a 0.24 dB SPL reduction in distortion-product otoacoustic emission levels[45]. Furthermore, histological analyses of presbycusis subjects demonstrated that, in the rat, age-related hair cell loss is predominantly of OHCs. The loss of inner hair cells ranged from 3.1% to 9.2%, while OHC loss ranged from 7.4% to 46.8%. Inner hair cell loss was greatest in the upper apex, while OHC loss was greatest at the basal turn[46].

General noise exposure is inevitable in modern life, which will eventually impair the auditory system, especially the OHCs. Abdala *et al* [33] found that the suppression tuning curve tip of distortion-product otoacoustic emission was exclusively elevated at 6 kHz in adults compared with younger subjects. They further showed that the adult subjects had audiometric air-conduction thresholds of < 15 dB HL from 500 Hz to 8 kHz. He suggests that the suppression tuning curve elevation at 6 000 Hz in adults may reflect general noise exposure and aging that results in partial hair cell loss in the basal portion of the adult cochlea. He suggests that using adults as the normal model of the mature cochlea is inappropriate. He further speculated that young children or pre-adolescents may better reflect a fully intact auditory periphery. The result of this study is consistent with that of Abdala *et al* [33], which suggests that the age of 6 years may be a turning point in age-dependent otoacoustic emission changes[5] and that children around 6 years old can suitably reflect a fully intact auditory periphery.

SNR changes with age

Our analysis showed that the rate at which total TEOAE levels decrease with increasing age is dependent on the frequency band. The maximum SNR frequency band shifts with age from higher frequency to lower frequency. Engdahl *et al* [8] also reported that the frequency band of maximum TEOAE levels decreased with age. However, the frequency band of maximum TEOAE levels in Engdahl *et al*'s report was lower than in the present review. Engdahl *et al* [8] showed that maximum TEOAE levels occurred at about 3 kHz in 3-day-old neonates, between 2.4 kHz and 3.4 kHz in 3 months old, at 2.4 kHz in 6 months old, and between 1.5 kHz and 2.4 kHz in

12 months old. Most other reports are consistent with our analysis[7, 11, 13, 15, 20, 29, 31].

The SNR in each analyzed frequency band also changed with increasing age. Significant negative correlations between SNR and age were found for the frequency bands ranging from 1.5 kHz to 4 kHz, although a statistically insignificant positive correlation between the SNR centered at 1 kHz and age was found (Figure 4). Significant negative correlations between spectral band amplitude and age have been reported for frequency bands ranging from 2.1 kHz to 5.1 kHz[6], which was consistent with our findings. Further, the SNR decreased with age more significantly in higher frequencies than in lower frequencies. A number of previous studies have also shown that the highest correlation between spectral band amplitude and age was at the frequency bands from 3.1 kHz to 4.6 kHz[6]. Moulin *et al* [22] reported TEOAEs from 270 ears from 135 normally hearing adults between 18 and 40 years old, and showed that the amplitude of the spectral bands decreased significantly as frequency increased above 1.4 kHz. This is evidence that the loss of OHC function in higher frequency bands is faster than in lower frequency bands. This may be the reason that the maximum SNR shifts from higher frequency to lower frequency bands with increasing age. These results also imply that the decrease in total TEOAE level with age is at least partially due to reduction of TEOAE energy, specifically in the mid- to high-frequency bands[6]. This is consistent with Yilmaz *et al* [48], who reported that the SNR in the 4 kHz frequency bands was significantly higher than in the 1 and 1.5 kHz frequency bands ($P < 0.001$) in neonates. In contrast, the SNR in the 4 kHz frequency bands were significantly lower than those in the 1, 2 and 3 kHz frequency bands ($P < 0.001$) in adults.

TEOAE spectrum peaks may relate to the resonance frequency of the ear canal. The resonance frequency of the outer ear canal can enhance the otoacoustic emission signal in the corresponding frequency. The major resonance of the external ear canal in neonates, 2-month-old infants and 6-year-old children was similar with the TEOAE spectrum peak. In neonates and 2-month-old infants, the TEOAE spectrum peak between 3.2 and 4 kHz was similar to the major resonance of the external ear canal. At birth, the ear canal resonance is higher, with a mean of 4.2–4.4 kHz. This decreases to a mean of 4.4 kHz at one month of age[40, 50]. In children aged 6 years or younger, the TEOAE spectrum peak at 3.2 kHz was similar to the major resonance of the external ear canal at 2.9 kHz. However, a discrepancy did exist. The age at which the frequency change occurred was different. TEOAE spectrum peak around 3.2 kHz was stable from neonate to 6 years old, but the major resonance of the external ear canal had already reached an adult-like mean of 2.9 kHz at 24 months of age. Second, the frequency of the TEOAE spectrum peak was lower than the frequency of ear canal resonance in subjects aged 9 years and older. The TEOAE spectrum peak shifted to 2 kHz in 9 years old[20] and to 1.5 kHz in 12 years old[21], whereas the major resonance of the external ear canal was still at 2.8 kHz in children aged 3–13 years and in adults[50-52]. Therefore, the TEOAE spectrum peak may only be related to the resonance frequency of the ear canal before 6 years old. After 6 years old, the TEOAE spectrum peak was independent of the resonance frequency of the ear canal.

Negative and positive pressure in the middle ear decreased overall TEOAE levels by an average of 4–5 dB SPL[53-54]. Negative pressure reduced TEOAE levels more than positive pressure[54]. There has been little research to test and analyze tympanometric parameters. Pressure in the middle ear likely affects the SNR at the frequency bands around 2 kHz and below for neonates and infants but may not correlate well with the age-related decrease of TEOAE amplitude. As reported, this decrease was most apparent at the 4 kHz frequency band as compared with the 1, 1.5, 2 and 3 kHz frequency bands ($P < 0.001$)[48]. On the contrary, the reduction of TEOAE levels induced by a change of middle ear pressure was greater for frequency bands at or below 2 000 Hz, and no changes were seen for 4 000 Hz[53-54]. Thus, the TEOAE level decrease was not associated with middle ear pressure[55]. Gvelesiani *et al* [56] analyzed the relationships of age and external and middle ear parameters with otoacoustic emission. They also demonstrated that external and middle ear parameters had no significant influence on otoacoustic emission. The age-related TEOAE spectrum peak shift is most likely because the OHCs functioning in higher frequencies are more prone to damage than those for lower frequencies.

Pure tone threshold (PTT) and TEOAE change with age

Literature regarding age-related changes in evoked otoacoustic emission is equivocal, mainly due to the difficulty distinguishing age-related reduction in evoked otoacoustic emission from the influence of hearing threshold deterioration. Some authors concluded that these changes are solely age-dependent[28, 44-45, 49], only caused by deterioration in hearing thresholds[27, 57-59], or the result of the combined effects of age and peripheral hearing loss[60]. Most of their results are correct, but the explanation of these results is imprecise. In fact, it was not difficult to distinguish between the effects of age and PTT on TEOAE. A good hearing threshold depends on efficient transmission of vibratory energy to the inner hair cells. It is to be expected that there will be a substantial correlation between otoacoustic emission and hearing threshold[40] but there is a lack of definite causality between otoacoustic emission rise and PTT decrease. Otoacoustic emission and PTT reflect different auditory mechanisms. The mammalian otoacoustic emission generation mechanism does not involve the inner hair cells that determine the local excitation threshold for activation of auditory nerve fibers[40]. Otoacoustic emission tests only reflect OHC function. That otoacoustic emission amplitude decreased with increasing age only demonstrated degeneration or loss of OHCs, which may result in PTT rise. However, PTT could remain unchanged if OHC loss and degeneration is in the normal or physiologic range. On the contrary, hearing thresholds deteriorated with increasing age not only because of OHC degeneration or loss, but also due to neural (ganglion-cell loss), metabolic (strial atrophy) and cochlear conductive causes (stiffness of the basilar membrane)[61]. Therefore, otoacoustic emission decease or OHC loss will not always lead to PTT rise. On the contrary, PTT rise will not always lead to otoacoustic emission decrease. Strictly, we can never say that otoacoustic emission decrease is because of PTT rise if we cannot demonstrate that the PTT rise is because of OHC loss or degeneration.

Stenklev *et al* [27] recorded TEAOEs in 90 year old female subjects with a PTT of 59.2 dB HL (present was 7.1%) and in male subjects aged 80–84 years with a PTT of 56.1 dB HL (present was 11.1%), using criteria of either overall response level of TEOAE better than 4 dB SPL or overall wave reproducibility of 55% or better. This is evidence that PTT deteriorated in these subjects not just due to OHC degeneration, because total loss of OHCs only results in a PTT increase of about 60 dB HL[1]. Therefore, PTT and otoacoustic emission change occur by different mechanisms during aging of the cochlea, as cochlear changes with age can happen *via* both OHC and stria vascularis degeneration.

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