The Onset and Development of Auditory Function: Contributions of Evoked Potential Studies

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Introduction

Hearing, albeit in the aquatic environment of the uterus, starts at around 5 1/2 months after conception, and the development of auditory function continues at least until the child leaves primary school. Thereafter parts of the auditory central nervous system continue to change. Thus, the auditory system may be plastic well into adulthood. This plasticity is bound to have an impact on any hearing induced cortical process, such as speech and language development. I write this review from the perspective that, in normal development, auditory evoked potentials will mirror the plasticity of the brain in their amplitude and latency changes. Abnormal development of hearing, caused either by transient or permanent hearing loss or by neurological deficits, is expected to be reflected in the way evoked potential parameters change with age. Behavioral assessment of the developing auditory system is not dealt with in this paper; the interested reader should consult Trehub and Schneider (1985) for a collection of papers.

In reviewing the development of hearing and the measurement of the related changes in evoked potentials I will consider three variables: the onset of auditory function, the rate of maturation of the various parts of the auditory system, and the point in time at which the various maturing mechanisms reach their adult values. We will investigate how the onset of hearing is measured and how it relates to maturation of cochlear structures. We will explore whether various parts of the auditory system mature in parallel, that is, at about the same time and with the same rate, or in a serial–middle ear first to cortex last–process in which the maturation of a more central structure depends on the level of maturation of more peripheral structures. Are there critical periods in hearing, that is, periods in which the developmental process is extremely vulnerable to environmental effects such as noise and ototoxic drugs? Can evoked potentials shed light on these maturation processes, and do they provide information about possible retardation in (auditory) development? How useful are evoked potential recordings in the neonatal intensive care unit (NICU) in predicting long standing conductive and permanent sensorineural hearing loss? In the following pages I will first try to address the majority of these questions briefly and then will go into more detail about the role of evoked potentials in the study of the development of hearing and the assessment of hearing function in neonates, infants, and children. I will review appropriate animal studies in so far as they are relevant for the interpretation of and extrapolation to human auditory development.

Deprivation and Critical Periods

In the following I will use the concept of a "critical period" that I define as "a period during which the action of a specific stimulus is required for normal development of the system, and during which the organism is maximally vulnerable to environmental manipulation." This is a combination of more restricted definitions (see Eggermont, 1986b). From studies in the visual system we know, for example, that deprivation of one eye or exposure to restricted patterns in certain critical periods can arrest, delay, or deteriorate visual function (Wiesel & Hubel, 1963). For instance, rearing cats in a vertical striped environment makes their visual cortex cells, after a while, insensitive to horizontal stripes. Patching one eye results in a dominance of the other eye, a phenomenon used to treat amblyopia (Blakemore, 1978).

Does an auditory counterpart of this visual deprivation exist? Experiments of middle/external ear ligation suggest that the effects of monaural deprivation may be species specific or restricted to certain brain stem nuclei and far more subtle than changes in the visual system (Rubel, 1978, 1985). For instance Kitzes and Semple (1985) studied the effect of unilateral cochlear ablation upon responses in the gerbil's inferior colliculus (IC). They found that responses from the ipsilateral part (with respect to stimulation) of the IC were very different from those in control animals. Instead of showing mainly inhibitory responses, most neurons were now excited by the stimulation. Reale, Brugge, and Chan (1987) studied the effects of unilateral cochlear ablation on responses in the cat auditory cortex. Again, responses were much more excitatory in ipsilateral cortex and had lower thresholds than in control animals. The effects were attributed to changes at the level of the brain stem.

With respect to these studies, we have to take into account that in primates and some other mammals the auditory system

is far enough developed to be exposed to sound in utero, while visual stimulation obviously does not occur. However, Brugge (1988) reports that certain brain stem mechanisms such as those responsible for interaural intensity and interaural time difference evaluation were unaffected in a cat with unilateral atresia of one ear canal. Cats are animals that are born virtually deaf, thus the argument of prenatal sound exposure is not the only explanation. In addition, the auditory system has extensive commissural fiber systems at the level of the superior olivary complex and the inferior colliculus, which are non-existent in the visual system. Thus, compensatory mechanisms have a greater chance in the auditory system than in the visual system.

Are there critical periods for the action of ototoxic agents on hearing, that is, are there periods in which the sensitivity to these agents is much larger than in adults? Transplacental ototoxicity in kanamycin treated pregnant guinea pigs (a species with a fully developed auditory system at birth) is dominant when administered in the period of onset and development of cochlear potentials. This constitutes by definition a critical period. It has been claimed that the period of maximum sensitivity to aminoglycosides in humans also coincides with the period of rapid cochlea development, the period which starts when the cochlea first responds to sound (18-20th week of gestation in humans) and ends when it has acquired most of its adult morphological and physiological properties (end of gestation to first post-natal month [Uziel, 1985; Pujol, 1986]). The evidence was based partly upon Bernard's (1981) results that in prematures receiving aminoglycoside treatment the wave V latency did not decrease with age (over a 10 day period) as it did in the non-treated control group. This prolongation of the latency, however, can hardly be the result of an ototoxic effect. It was reported that the normal control group showed an expected decrease in the wave V latency of about 1-1.5 ms, while the treatment group did not show any latency change. If this relative increase in latency in the treatment group were due to a high frequency sensorineural hearing loss, it would require at least the complete destruction of the region down to 1 kHz, and such profound hearing losses have, to my knowledge, not been found in aminoglycoside treated neonates. Another possibility is that aminoglycosides arrest the development of hearing; however, since no wave I-V interval values were reported in Bernard's paper, clear evidence in favor of this idea cannot be provided. It is much more likely that the neonates were given aminoglycosides because of a lesser general health. It has been shown that reduced wellness favors the probability of middle ear pathology, which can easily account for the observed latency differences. Thus, at present the evidence for a critical period for aminoglycosides in human neonates, except by analogy with other species, is not conclusive.

Noise in neonates is claimed to be damaging at levels (60-70 dB) that do not harm adults (Bock & Saunders, 1977; Douek, Bannister, Dodson, Ashcroft, and Humphries, 1976). Again there is a critical period starting after the apparent structural maturation of the cochlea, in humans say from 7-8 mo conceptional age. There may be an overlap with a sensitive period for aminoglycoside ototoxicity (if it exists) resulting in a possible potentiation of these two effects under conditions that involve both moderately high noise levels (about 70 dB SPL) and aminoglycoside administration. In all probability this effect will be counter balanced in most neonates by the high incidence of middle ear effusions and the accompanying conductive hearing loss, possibly explaining why the findings of acquired high frequency hearing loss in NICU graduates are relatively modest. It should be noted that Bernard and Péchère (1984) failed to show a potentiation effect of noise and aminoglycosides in newborn rats.

Effects of sound deprivation in the first two years of life, as a result of recurrent otitis media or, more likely, middle ear effusions, upon various aspects of language acquisition such as verbal ability, auditory decoding, and spelling skills have been reported (Sak & Ruben, 1981; Webster, 1983; Perier, Alegria, Buyse, D'Alimonte, Gilson, and Serniclaes, 1984). These peripheral abnormalities might cause abnormal slow vertex potentials (SVPs). Cone-Wesson, Kurtzberg, and Vaughan (1987) report that the incidence of SVP abnormality is three times more common in babies with bilaterally elevated ABR thresholds than in those with normal hearing or mild unilateral hearing loss. Explanations may run as follows: "A delay in the maturation of the cortical areas concerned with the acoustic analysis of speech might result in impaired development of environmentally dependent mechanisms of auditory processing" (Kurtzberg, Hilpert, Kreutzer, and Vaughan, 1984). Thus "the early childhood capacity to make phonetic distinctions must seemingly be stimulated by the corresponding sound in spoken language; children with a congenital or early acquired hearing loss might loose this early competence" (Perier et al., 1984). And "it may be hypothesized that delayed maturation of cortical synaptic mechanisms, from whatever cause, could impede the normal interaction between auditory stimulation and the neurophysiological substrate of cortical auditory processing" (Kurtzberg et al., 1984).

Onset of Auditory Function in Humans

Human Data

Since auditory function in humans starts well before birth, the onset has to be determined in the uterus. By measuring the eye blink reflex of fetuses with high resolution ultrasound imaging techniques, Birnholz and Benacerraf (1983) showed that, in all cases, fetuses older than 29 weeks showed a response to sound of 110 dB SPL delivered to the abdominal wall of the mother. The SPL was measured two inches away from the transducer

in "free field"; the sound had two dominant spectral peaks at 250 and 850 Hz. Assuming that the attenuation through the maternal abdominal and uterine walls is at least 20 dB in this frequency range and that the background noise in the uterus in this frequency range is about 75 dB SPL (Rubel, 1978), the stimulus is probably not much more than 20 dB above the noise level. In no case was there a response when the fetus was younger than 24 weeks. Modification of the fetal heart rate by sound, however, has been reported to start in the 20th week, but becomes more consistent around the 24th week (Bench & Metz, 1974). In prematures around the 25th week, the N1, P2 complex of the slow vertex potentials (SVPs) can be measured (Weitzman & Graziani, 1968) and also the auditory brain stem responses (ABR) can be recorded (Starr, Amlie, Martin, & Sanders, 1977). These results are related to anatomical findings showing that at a fetal age of 25 weeks the cochlea has attained its final size although not its functional maturity (Bredberg, 1985). Myelination of the auditory nerve starts in the 22nd week (Lavigne-Rebilard & Pujol, 1988).

Supporting Animal Studies

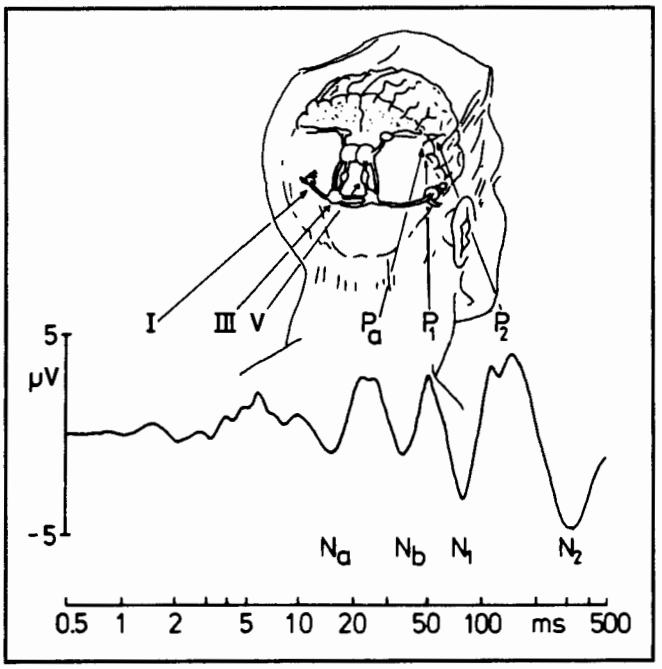
It seems that at the moment the cochlea starts functioning, other parts of the central nervous system (CNS), as revealed by evoked potential measurement, are capable of signaling that function. This indicates either that the cochlea is the limiting factor or that the auditory system matures in parallel fashion. However, in the cochlea there definitely is some serial development in the differentiation of the hair cells that begins in the first half of the basal turn and then progresses towards the base as well as the apex, the latter matures about two weeks after the base (Lavigne-Rebilard & Pujol, 1988). Some cochlear structures mature at different rates. Inner hair cells and most of their synaptic connections are mature before the outer hair cells. Almost adult-like connections between inner hair cells and auditory nerve fibers (afferent synapses) are present before the onset of cochlear function. In contrast, the connections between efferent fibers (descending from the brain stem) and the hair cells appear well after the onset of function but seem to be necessary for sharp tuning of the auditory nerve fibers (Pujol, 1985). Before the onset of auditory function, the whole auditory pathway is ready to function except for its hair cells, which seem to be the limiting factor. Miyata, Kawaguchi, Samejima, and Yamamoto (1982) showed that in the kitten, from birth on, evoked potentials can be recorded from the auditory cortex upon electrical stimulation of the cochlear nucleus. At that age, sound stimuli have to be over 110 dB SPL to produce any measurable evoked response. Walsh and McGee (1986) showed that the number of myelin lamina surrounding the auditory nerve fibers in the kitten needs about 6 months to reach mature levels. By comparing the changes in the myelination with the decrease in wave I latency and observing that these did not follow the same time course, they concluded that "myelination is not the major process influencing the development of evoked potentials generated within the auditory nerve." Assuming an exponential increase in length, presumably correct in the initial phase of the myelination, then one expects a hyperbolic decrease in latency for the initial phase of the myelination process (Eggermont, 1988). A linear increase in diameter will result in a logarithmic increase in conduction velocity, and thus latency will be inversely proportional to the logarithm of the diameter. Obviously the conduction velocity in the auditory nerve fibers is not linearly related to the number of myelin lamina isolating them from other nerve fibers. Thus the more or less linear increase in the number of lamina found by Walsh and McGee (1986) will result in a very rapid decrease in the wave I latency. We have, however, to take into account that changes in the inner hair cell auditory nerve fiber synapse are occurring as well.

In contrast to anatomical development, which begins at the base of the cochlea, behavioral and electrophysiological reactions to sound at about the end of week 24 are reported to start at the low frequencies, while responses to frequencies above 3000 Hz do not start before week 30 (Rubel, 1978). In order to explain this discrepancy, Rubel, Lippe, and Ryals (1984), on the basis of acoustic trauma studies and receptive field mappings in midbrain nuclei of chicken hatchlings and adults, postulated the "shifting place" principle. This idea–that because of the increasing stiffness of the membrane with age, the basilar membrane in the newborn at a certain point is tuned to a lower frequency than in the adult–can explain some of these discrepancies. Corroboration for the Mongolian gerbil came from Ryan and Woolf (1988), who showed changes with age of the tonotopy in the dorsal cochlear nucleus. Arjmand, Harris, and Dallos (1988) demonstrated in the gerbil cochlea about a 1.5 octave upward shift in the characteristic frequencies in the mid basal turn but could not demonstrate any change in the second turn. However, data in chicks arguing against the theory of Rubel have been published as well (Manley, Brix, & Kaiser, 1987). Thus, evidence for changes in the tonotopic organization is clear, but the complete mechanism is far from understood. With respect to human development, an equivalent period of changing tonotopy will probably be found in the third trimester.

Auditory Evoked Potentials

Auditory evoked potentials (AEP) come in various sorts and varieties. They originate in the cochlea (cochlear microphonic [CM] and summating potential [SP]), the auditory nerve (compound action potential [CAP] and waves I and II of the ABR), the auditory brain stem (waves III to V of the ABR), the auditory midbrain and/or thalamus (waves VI and VII of the ABR), and the auditory cortex (middle latency responses [MLR] and SVPs.) Figure 1 shows a series of evoked potential components (ABR, MLR, and SVP) on a logarithmic time scale with an indication of the possible generation sites.

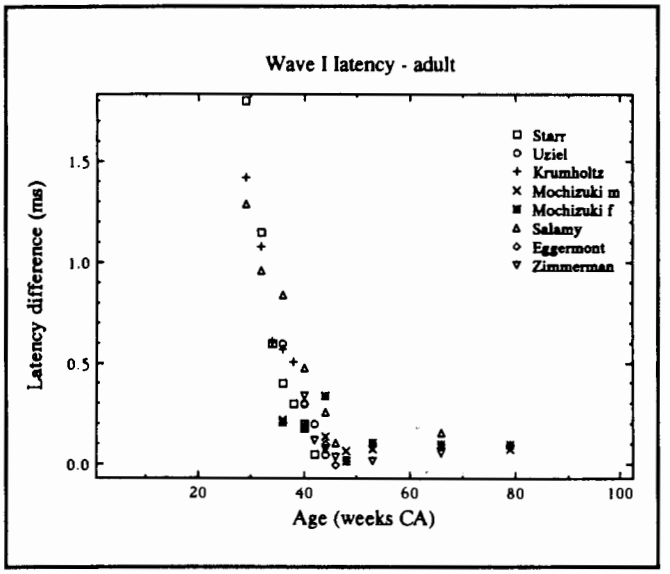
Figure 1. Logarithmically compressed series of auditory evoked potentials, showing the ABR (waves I, III, and V) in the first 10 msec after the stimulus onset, the MLR (waves N_a, P_a, and N_b) from 15 to 50 msec, and the SVP (P_1 through N_2). The most likely generator sites for each of the waves is indicated. Two groups can be distinguished: Generators for latencies less than 10 msec are in the auditory nerve (wave I) or in the brain stem (waves III and V), generators for the MLR and SVP are in primary and secondary auditory cortices.



Depending on the type of stimulus used, we can distinguish the transient AEPs (click and tone pip evoked: the CAP, ABR, MLR, and SVP) and the continuous AEPs (FFR and 40 Hz MLR). The more rostral the origin of the AEP, the longer is its latency; thus, for a 60 dB nHL click, the CAP (and also wave I) has a latency of about 1.6 ms, wave V (probably originating in the lateral lemniscus) has a latency of 5.6 ms, the P_a component of the MLR is 25 ms, and that of the N_1 component of the SVP, about 90 ms. These latencies are not only dependent on stimulus intensity (they decrease for increasing intensity) but also upon the frequency of the tone (at low intensities one finds longer latencies for lower tone frequencies). Repetition rate affects the latencies as does background noise masking (faster rates and higher noise levels result in longer latencies). Filter settings in the recording system also can affect latency (Stockard & Stockard, 1983). A comprehensive survey of the use of the ABR in pediatrics has been given by Picton, Taylor, Durieux-Smith, and Edwards (1986).

Besides these experimental factors there are subject factors that influence AEP latency. One of the most common is auditory or neural pathology such as middle ear impairment, a high frequency sensorineural hearing loss, the presence of an

Figure 2. Differences with adult latency for wave I as a function of conceptional age. Data are based on mean values from various publications, indicated by first author; the additions *m* and *f* after Mochizuki represent male and female subjects. The Eggermont data refer to Eggermont and Salamy (1988a).



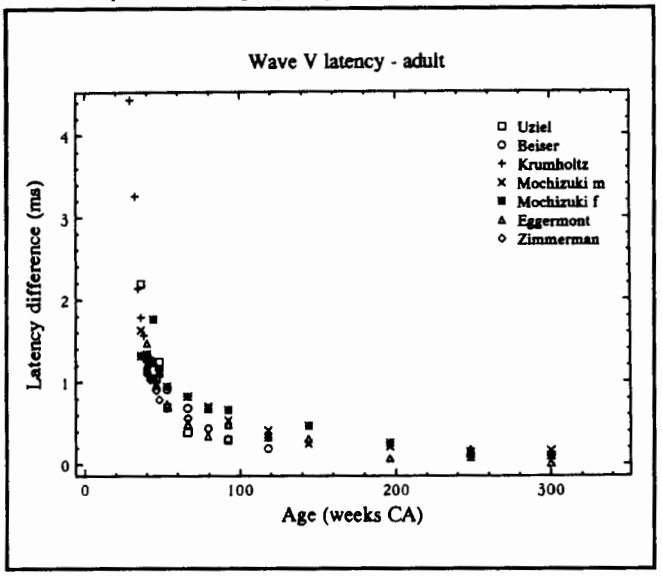
acoustic neuroma, or multiple sclerosis. All these factors increase the latency of the brain stem potentials by values in the order of a millisecond. In addition, the neurological impairments increase the latency difference between various waves in the ABR (e.g., the wave I-V interval). Gender is known to affect ABR latencies; females have shorter peak and inter-peak latencies than males (Stockard & Stockard, 1983), which already becomes evident in the first few years of life (Mochizuki, Go, Ohkubo, & Motomara, 1983). This gender effect cannot always be demonstrated in infants (Durieux-Smith, Edwards, Picton, & McMurray, 1985). Part of the effect in adults can be explained by differences in head size (Trune, Mitchell, & Phillips, 1988). Age affects latencies as well; neonates have longer latencies than adults. This aspect of the AEPs has been explored extensively, and the remainder of this paper will deal with these changes and what they tell us about the maturation of the brain and the development of auditory function.

Latency Changes in AEPs During Normal Development

A Simple Model for Developmental Changes

I have made several assumptions with regard to developmental changes in AEPs (Eggermont, 1985a, 1988). These are that: (1) latency changes seen for each of the evoked potentials reflect the maturation of structures (in the cochlea, auditory nerve, brain stem, and up to the auditory cortex) that are

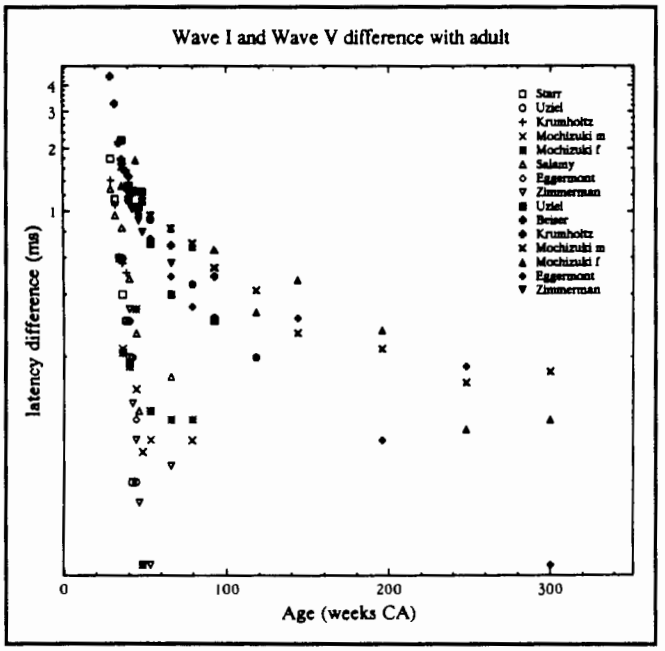
Figure 3. Differences with adult latency for wave V as a function of conceptional age. Data again represent mean values at particular age groups from various publications.



peripheral to its proposed generation site (thus changes in the wave V latency will depend on changes in the cochlea, auditory nerve, and the lower brain stem up to the level of the lateral lemniscus); (2) maturation of auditory system structures is mainly the result of increased myelination (especially in auditory nerve and brain stem), increases in synaptic density (mainly in auditory cortex), and increases in synaptic efficacy (everywhere); (3) each of these increases results in an exponential decrease in latency of the evoked potentials but with different time constants (or specific maturation rates); (4) all maturational processes proceed independently and thus in parallel; and (5) the resulting latency changes from all these maturational processes can be described as the sum of decreasing exponentials. In the following sections, the dependence of latency on conceptional age and some aspects of gestational age will be discussed. For that purpose, the definition of both terms is given here: Gestational age is the age in weeks between conception and birth, and conceptional age is the age in weeks between conception and time of testing. Thus, for each infant only one gestational age applies, however, it can be tested at a series of conceptional ages (see also Gorga, Reiland, Beauchaine, Worthington, & Jesteadt, 1987).

Changes in wave I (the compound action potential of the auditory nerve) can hardly be observed in the full term infant, suggesting that the cochlea is very close to maturity at the time of full term birth, and, in order to study these changes, we have to rely on preterms (Eggermont & Salamy, 1988a). In selecting the preterm group for the purpose of studying the changes in wave I, or for that matter in any of the absolute peak latencies, we have to be careful to avoid conductive hearing losses. Such hearing losses caused by otitis media or middle ear effusion,

Figure 4. Differences with adult values for wave I and wave V on semi-logarithmic coordinates. In this particular representation exponential functions become straight lines. The data suggest that the changes in wave I (open symbols or thin symbols) are exponential. However, the wave V data (closed or fat symbols) are apparently not on a straight line and thus require at least two exponential functions to characterize them.



which is very common in preterm infants (Balkany, Berman, Simmons, & Jafek, 1978), will increase the latency of wave I. Because of the fluctuating nature of such hearing losses, these latency changes interfere in an unpredictable way with the latency decrease caused by the maturation process. To obtain an accurate impression of age dependent latency changes one should preferably compare studies from various institutions in order to avoid sample bias. One difficult aspect to deal with is that different clinics rarely employ the same equipment or the same filter settings, headphones, or stimulus levels. Thus, only the differences in the latency with adult values (determined in the same clinic with the same equipment) as a function of conceptional age will be considered here. This then will only represent the effect of maturation. In Figure 2 such a plot is shown; latency differences with adult values are plotted as a function of conceptional age. One observes that maturation of wave I for clicks is finished somewhat around the 45th week conceptional age and that from full term birth on there is only a small difference with adult values. Therefore, one can say that in the full term infant slightly after birth, the cochlea (at least the basal part thereof) and auditory nerve are fully mature.

Changes in wave V latency are expected to follow in part the changes in wave I latency and, in addition, to reflect the maturation of the auditory brain stem structures. The latency

Figure 5. Difference with adult values for the I-V delay as a function of conceptional age. In this semi-log plot we observe the same basic patterns as for wave V: The data do not fall along a straight line and thus require more than one exponential function to describe them.

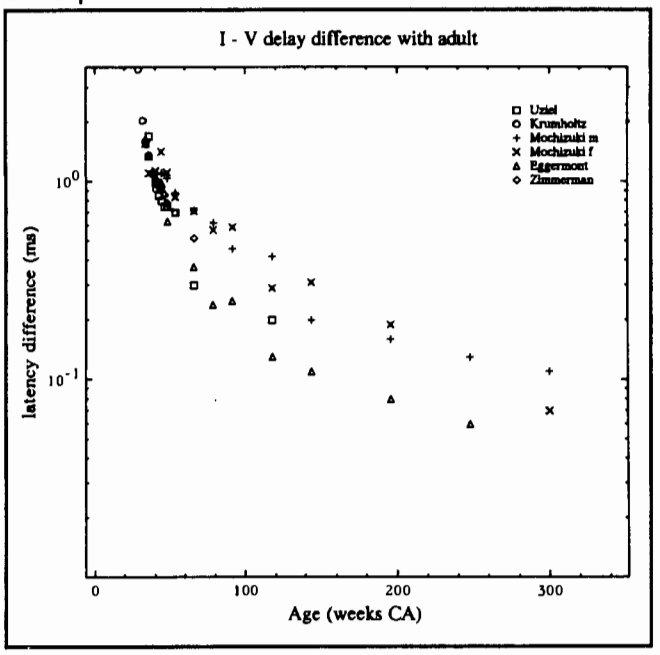
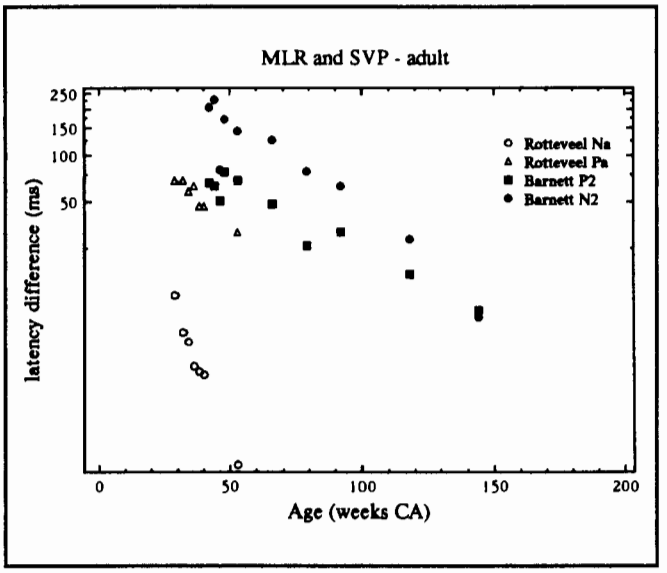


Figure 6. Differences with adult values for some MLR and SVP data. The data suggest that the N_a and P_a components mature at a different rate but that the SVP components mature with the same rate as the P_a component of the MLR. The quite different age spans of the two investigations preclude any detailed conclusion.

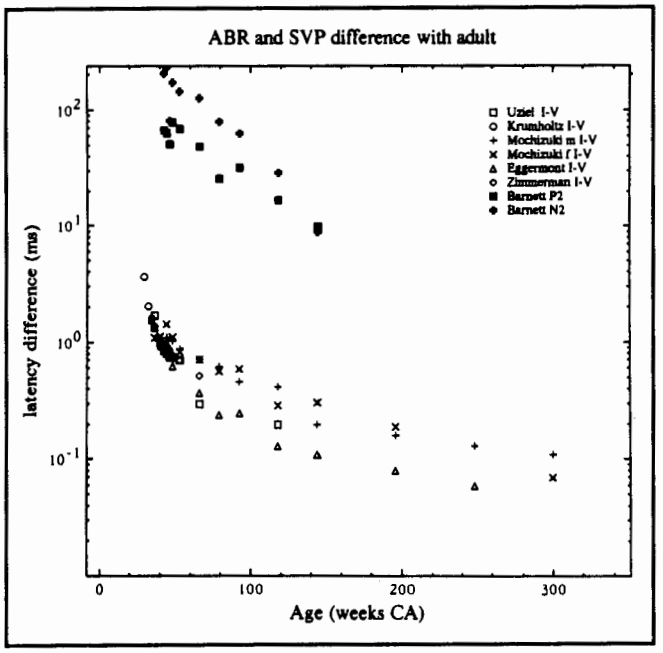


differences with the adult values are plotted in Figure 3. One observes that it takes approximately 3-5 years for this difference to become negligibly small. Plotting the available data for wave I and wave V as a function of conceptional age on semi-log paper (Figure 4) shows that the latency points for wave I scatter around a straight line, which is an indication that the latency changes are occurring in an exponential way (at each age the decrease in latency is a fixed percentage of the latency at that age). For wave V, an approximation by one straight line is no longer possible; clearly there is more than one exponential process. It appears that the curve through the data points can be approximated very well by the sum of two exponential functions. One of these exponential functions has, as expected, the same slope as that for the wave I changes. The other line with a much shallower slope, and therefore representing a much slower process, is assumed to reflect the brain stem related changes.

Changes in the I-V delay are assumed to depend only on the maturation of the brain stem structures, because changes in the auditory periphery supposedly affect waves I and V in an identical way. Plotting the differences with adult I-V delay as a function of conceptional age (Figure 5) shows that even in this case the data cannot be fitted with one exponential. Two exponentials again suffice to describe the findings. The slower process has the same slope as for wave V; the residual fast process has a time constant (slope of the curve) comparable to that for the maturation of wave I. This indicates either that the I-V delay is not only reflecting brain stem processes but also cochlear ones, or that in brain stem maturation a fast process is also present. These changes in the I-V interval in healthy infants are only dependent on conceptional age and not on gestational age (e.g., Gorga et al.,1987).

Changes in the MLR components in infancy and childhood have been somewhat controversial; some investigators could not find reliable latency changes (e.g., Kraus, Smith, Reed, Stein, & Cartee, 1985) while others claim, and their data seem to support it, that consistent latency changes can be recorded but not in all subjects (Rotteveel, Colon, Stegeman, & Viseo, 1987; Suzuki & Hirabayashi, 1987). Although the adult reference data in the former reference are not provided, searching through the literature and a few trial and errors to find the "correct" value for this particular data set, resulted in changes with adult latency that basically show the same rate of change as for wave V. Recent data from Suzuki and Hirabayashi (1987) indicated that the P_a component of the ABR has barely reached maturity in the 12-14 year old. In Figure 6 the data are plotted in the usual fashion to show the similarity with the rate of maturation of the ABR. Care must be excersised with respect to the interpretation of changes in the 40 Hz EP with age, which can be considered as a convoluted addition of the P_o (actually wave V of the ABR) and the MLR components. While the ABR is usually present in all infants, but the MLR is not, the 40 Hz EP can in such cases only be composed of the ABR component resulting in very low plitude and of course providing no additional information to the ABR.

Figure 7. Differences with adult values for I-V delay and SVP components as a function of conceptional age. It appears as if the cortical components mature at about the same rate as the brain stem potentials and definitely not slower.



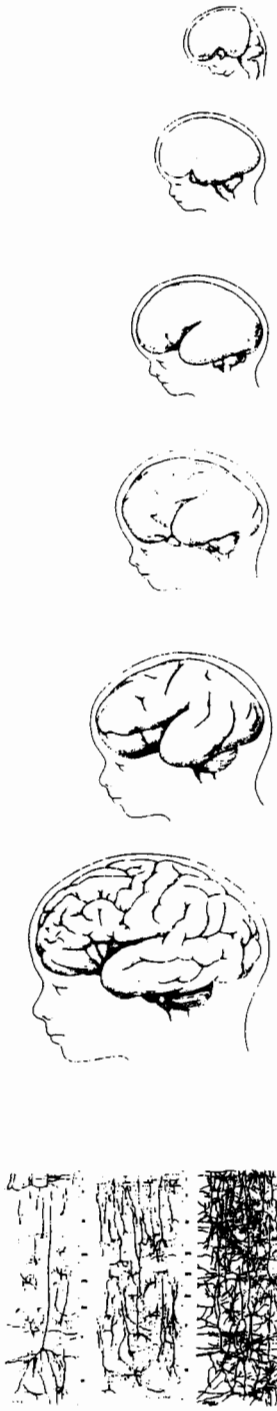
Changes in the SVP components, N_2 and P_2, can be shown on the basis of the data of Barnett, Ohlrich, Weiss, and Shanks (1975) covering the time span of 3 days after birth to 3 years of age. The rate of change again was found to be about the same as for the ABR wave V (Figure 6, 7). Thus we can definitely rule out that the maturation of these SVPs is governed by a slower process than that for the ABR. SVPs were studied as a function of age in very low birth weight (VLBW) and normal full term infants (Kurtzberg et al., 1984) using 800 Hz tone pips and /da/, /ta/ syllables. Normal full terms had a higher proportion of mature responses than the VLBW infant; at age 1 mo up to half of the VLBW infants had not achieved a mature response. Midline responses (Heschl's gyrus, primary auditory cortex) matured earlier than laterally recorded responses (secondary cortical areas). This parallels the findings of Saintonge, Lavoie, Lachapelle, and Cote (1986) who observed in small-for-date neonates (birth weight in lower 10 percentile) a significantly prolonged I-V delay as compared to conceptional age matched controls.

Roughly speaking at least two processes (and most likely three, see Eggermont, [1988]) can be distinguished in the maturation of auditory evoked potentials. These processes probably reflect myelination and synaptic density and efficacy increases or combinations thereof and are characterized by the short and the long time constant. They are sufficient to describe the maturational aspects of all AEPs from cochlea to auditory cortex (see Eggermont, [1988] and Eggermont and Salamy, [1988a] for details about the way the possible mechanisms relate to the time constants). The rate of change in latency, therefore, is roughly the same in the ABR, the MLR, and the SVPs. This rate of change does not tell the complete story, however. Another important aspect is at what age the latencies of the various AEP components reach adult values. This information can be obtained from the intercept with the time axis of the exponential functions at a prespecified value of the latency difference (say about 1% of the initial difference). The results are shown in Figure 8 where anatomical, morphological, physiological, and behavioral data related to the development of hearing in humans have been compiled. One observes that the maturation point shifts to longer values for more central generators.

Comparison of various ABR studies reveals that there is a surprisingly good correspondence between our own and other published results (see Figures 2, 3, 4, and 5). Part of the reason for the good correspondence is that comparisons were made for differences with respect to adult latency data obtained in the same laboratory, and so to a large extend eliminate idiosyncratic effects of stimulus and equipment. On other occasions (Eggermont, 1985a, 1986a) data were selected from other publications, only some of which are included in the present study. One particularly interesting study (Teas, Klein, & Kramer, 1982) also used tone-pips in addition to clicks to study the maturational time course. The results for 8 kHz tone-pips are quite comparable to the click data reviewed here. However, the 1, 2, and 4 kHz tone-pip data suggest that for lower frequencies the rate of maturation is faster. As a result adult values are reached earlier for low frequency stimuli. Whether this reflects the earlier responsiveness for low frequency sound or is a peculiarity of the stimuli used is currently under investigation in our lab using clicks and the derived-response technique (Don, Eggermont, & Brackmann, 1979).

The later potentials have received less attention so comparison is not always possible. For the MLR, there are only two studies (Rotteveel et al., 1987; Suzuki & Hirabayashi, 1987) that are quite contrasting. On the basis of an estimate of adult latencies for the Rotteveel et al. study, the data shown in Figure 6 were calculated; these data suggest that the N_a component latency reaches adult values at around 50 weeks CA, while for the P_a component this happens at a much later time. Results from Suzuki and Hirabayashi (not shown) suggest that this P_a latency takes 12-14 years to mature. It is difficult to believe that the two components differ so much in their maturational pattern; thus, either the estimate of the adult value was wrong to a large amount or the data are in that respect still unreliable.

Figure 8. Time lines for human development. The gross developmental changes that take place in the brain and cochlea are illustrated through schematic changes in the cortex. It should be realized that the limiting factors in the functioning of the auditory system, as given in the right hand side, are all located in the cochlea and its innervation. After full term birth, developmental changes occur in the myelination of the auditory nerve and brain stem tracts, and in the connections between cells in the cortex. This is exemplified by three views of the cortical dendritic network (at birth, 3 months, and about 2 years). Graphics after Conel (1959) and Cowan (1979).



time lines for human development

3 mo:
- first afferent nerve endings to ihc and ohc can be seen (Lavigne-Rebillard and Pujol, 1988),
- no sign of myelination

4 mo:
- ihc are fully developed (Bredberg, 1985)

5 mo:
- ohc developed in the basal and middle turn (Bredberg, 1985),
- efferents contact base of ohc at 14 weeks,
- myelination of most nerve fibers starts (Lavigne-Rebillard and Pujol, 1988)
- onset of cochlear function between 16 and 22 gestational week (Pujol, 1985)
- modification of the fetal heart rate is possible (Bench and Metz, 1974)

6 mo:
- cochlea attains final size (Bredberg, 1985),
- myelination of spiral lamina fibers and efferent ohc synapses still incomplete (Lavigne-Rebillard and Pujol, 1988)
- CM and SP appear (Pujol and Uziel, 1988)
- ABR recordings become possible (in prematures)
- Slow vertex potentials appear as well (Weitzman and Graziani, 1968)

7 mo:
- fetus makes movements in reaction to sound
- all fetuses show eye blink reflexes
- mature cochlea (Pujol, 1985)

8 mo:
- cochlea is complete adult like (Bredberg, 1985)

9 mo:
- CM and SP mature (Pujol and Uziel, 1988)
- middle ear functionally mature (Saunders et al.,1983)

——FULL TERM BIRTH——

1 mo
- auditory nerve response mature

5 yr:
- ABR adult like

14 yrs:
- MLRs mature

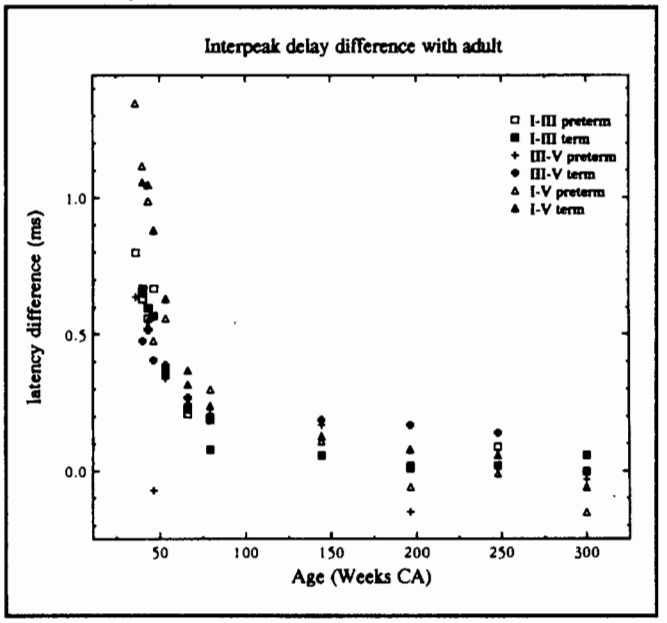
14 yrs:
- slow vertex potentials mature

20 yrs:
- P300 mature

Is Auditory Maturation Affected by Prematurity and Complications in Early Life?

Recently Eggermont and Salamy (1988a,b) investigated the maturation of the ABR for a group of full terms (N=465) and a group of healthy preterms (N=178). The preterm population had birthweights equal to or below 1500 grams (*mean* = 1097, SD= 223.94) and gestational ages ranging from 25-35 weeks (*mean* 29.3, SD= 2.3). All subjects were enrolled in the Pediatric Follow-up Program at UCSF. Infants with chromosomal abnormalities or major congenital anomalies, significant neurological involvement, or hearing loss (determined retrospectively), were excluded from ABR analyses. The study was mixed longitudinal and cross sectional (total number of ABRs=1164) and demonstrated that the I-III, III-V, and I-V delay changed in the same way in preterms as in full terms (Figure 9) and that the actual value of these delays was determined by the conceptional age and was independent of gestational age. Furthermore the rate of change appears to be the same for all three inter-peak intervals. Thus prematurity has in itself no adverse effect on the maturation of ABR parameters, and the earlier exposure to environmental sounds does not advance the maturation of the ABR.

Figure 9. Differences with adult values for the interpeak delays I-III, III-V, and I-V as a function of conceptional age for a preterm and a full term population. Mean age group values (Eggermont & Salamy, 1988a) are plotted. One observes that the rate of maturation is the same for the auditory nerve (I-III) and for the lower brain stem (III-V) as well as for preterms and full terms.



At the Banff CASLPA conference (1988) some findings were presented (Eggermont et al., to be published) about the effect of the general health status of the preterm in the NICU on the development of ABR parameters. Two hundred and twenty-four (224) VLBW infants requiring intensive care in the nursery served as subjects in this prospective study. All subjects had birthweights between 520 and 1500 grams (*mean* = 1036, SD = 226), and ranged from 24-34 weeks (*mean* = 28, SD = 2.1) gestation. It appeared that regardless of the health status of the neonate, the I-V interval was enlarged at 40 weeks CA but was the same as in the full term controls at the age of 3 years. Neonates that were less healthy showed a higher incidence of middle ear effusions, had a higher incidence of sensorineural hearing loss, suffered from long lasting neurological disorders, and scored lower on mental capacity tests later in life (Salamy, Eldredge, & Tooley, 1988). It seems as if the maturation of the auditory brain stem is a highly autonomous and rigid process that, in contrast to cortically related phenomena, is not permanently affected, save for malnutrition, by ill health in NICU. Thus we will have to rely on the evoked potentials of cortical origin such as the MLR and the SVPs to monitor developmental abnormalities.

Hearing Tests in NICU and Necessity of Follow-up

It has become common practice to test all graduates of the NICU with ABR as a screening for hearing loss (Durieux-Smith & Picton, 1985). This screening results in a 'pass' when there are clear ABRs for a 30 dB nHL click. This, as common lore will, excludes more than a slight hearing loss, but is this really the case? In adults, click thresholds, whether for the compound action potential (the electrocochleogram) or for wave V, correspond best with the average hearing loss at 2 and 4 kHz (Eggermont, 1976; Parving & Elberling, 1982; Van der Drift, Brocaar, & van Zanten, 1987). The latency intensity function and the click threshold are not affected by a slight high frequency hearing loss (up to 40 dB at 8 kHz, up to 20 dB at 4 kHz), so usually these losses go unnoticed. Neither the click threshold nor the latency intensity function are changed by a moderate low frequency hearing loss (up to 40 dB at 1 kHz, up to at least 60 dB for lower frequencies), so such hearing losses are missed as well. The preterm infant is very prone to recurrent otitis media (estimates run from 30% [Balkany et al., 1978] to 67% [Hooks & Weber, 1984] of the newborns in NICU). Thus the ABR threshold at discharge is not indicative of a permanent hearing loss. A more effective way of estimating only the sensorineural hearing loss component may be the use of bone conducted sounds (Hooks & Weber, 1984). From the neonates who are at risk, usually 10-15% fail the ABR test at discharge from the NICU; retest of the fail cases results ultimately in a persistent hearing loss in 2-4% of the at risk cases (Cevette, 1984; Sanders, Durieux-Smith, Hyde, Kilney, Jacobson, & Murnane, 1985; Murray, Javel, & Watson, 1985; Picton et al., 1986; Riko, Hyde, & Alberti, 1985). It is impractical to retest all 'pass' cases (es-

timates are that 3% of the newborns tested may be false negatives, i.e., passing the test but having a partial hearing loss), but this population may well contain mild high frequency sensorineural hearing losses and pronounced low frequency hearing losses.

The click ABR threshold undergoes small changes in the course of development, from about 30 dB nHL at full term birth to 10 dB nHL around two years of age (Kaga & Tanaka, 1980; Picton et al., 1986). As we have seen, latencies and the latency-intensity functions undergo pronounced changes during development and thus interfere with a finely tuned diagnosis.

These remarks on screening in NICU are meant to indicate how difficult the interpretation of ABRs at discharge from the NICU is, not to argue against the use of ABRs in NICU. We should keep in mind that there will be false positives and false negatives in the results of the screening. False negatives should be avoided as much as possible, but this usually can only be done at the expense of an increase in the number of false positives. For a better validation, follow-up ABRs, preferably with tone pip stimuli combined with a behavioral analysis, should be carried out at about 3, 6, and 9 months adjusted age (or equivalently at 53, 66, and 79 weeks conceptional age). From this time series analysis, reasonably solid conclusions can be drawn with respect to the presence of permanent hearing loss.

In order to improve the predictive power of the ABR with respect to the future audiogram, tone pip (Alberti, Hyde, Riko, Corbin, & Abramowich, 1983) or click with high pass noise masking (Don et al.,1979) stimuli should be used. From our experience with tone pip electrocochleography in infants and the comparison with audiometric thresholds at a later age (Spoor & Eggermont, 1976), we expect that tone pip ABR in infants will be accurate as well as reliable. Because the potentials are quite small as compared to those in electrocochleography, testing duration will be longer, and because of the rather broad potentials for low frequency tone pips, one may wish to use MLRs (when they can be obtained), which are generally larger for the lower frequencies. Kileny and Magathan (1987) compared click and 500 Hz tone pip ABR thresholds with the first reliable pure-tone audiogram in preschool age children enrolled in a program for the hearing impaired. No false positives were found in the group of 35 ears studied. It was found that there was no one-to-one relationship between the electrophysiologic threshold and the behavioral ones. The click threshold underestimated the severe hearing losses with respect to the milder ones, while the 500 Hz tone pip thresholds were on average 20 dB below the subjective ones at that frequency.

The use of MLR and SVPs presents important additional information beyond screening with the ABR. This has most forcefully been documented by Cone-Wesson et al. (1987) who showed that in 50 cases (VLBW infants 3-12 mo) in which the ABR I-V interval and the wave V to wave I amplitude ratio were normal, nine had abnormal cortical responses. This usually manifests itself in the MLR as missing components.

Conclusions

Maturation of the auditory system is a long process, composed of several identifiable stages that reflect the development of specific structural parts such as synapses and myelin. Most changes proceed in parallel at all levels in the auditory system. These changes can be documented in humans using the various types of evoked potentials and studying their latencies as a function of age. It is not clear at present that there are measurable effects of sound deprivation or ill-health on the maturation of the auditory brain stem. At the cortical, speech processing level, definite interference has been shown. Because of the susceptibility of the NICU resident and graduate to otitis media, measurements in NICU to predict the possibility and amount of permanent hearing loss are usually not very reliable when done only with click ABR and have to be followed up by more frequency specific measurements using, for example, tone-pip ABR. Despite its shortcomings, the click ABR is the only reliable screening procedure that is presently available. In combination with follow-up ABR-studies in the first year of life, it is expected that a reliable prognosis about hearing capacities in later life can be made.

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