Clinical Neurophysiology 118 (2007) 676–689

www.elsevier.com/locate/clinph

The pattern of auditory brainstem response wave V maturation in cochlear-implanted children ☆

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Accepted 8 November 2006
Available online 16 January 2007

Abstract

Objective: Maturation of acoustically evoked brainstem responses (ABR) in hearing children is not complete at birth but rather continues over the first two years of life. In particular, it has been established that the decrease in ABR wave V latency can be modeled as the sum of two decaying exponential functions with respective time-constants of 4 and 50 weeks [Eggermont, J.J., Salamy, A., 1988a. Maturational time-course for the ABR in preterm and full term infants. Hear Res 33, 35–47; Eggermont, J.J., Salamy, A., 1988b. Development of ABR parameters in a preterm and a term born population. Ear Hear 9, 283–9]. Here, we investigated the maturation of electrically evoked auditory brainstem responses (EABR) in 55 deaf children who recovered hearing after cochlear implantation, and proposed a predictive model of EABR maturation depending on the onset of deafness. The pattern of EABR maturation over the first 2 years of cochlear implant use was compared with the normal pattern of ABR maturation in hearing children.

Methods: Changes in EABR wave V latency over the 2 years following cochlear implant connection were analyzed in two groups of children. The first group ($n = 41$) consisted of children with early-onset of deafness (mostly congenital), and the second ($n = 14$) of children who had become profoundly deaf after 1 year of age. The modeling of changes in EABR wave V latency with time was based on the mean values from each of the two groups, allowing comparison of the rates of EABR maturation between groups. Differences between EABRs elicited at the basal and apical ends of the implant electrode array were also tested.

Results: There was no influence of age at implantation on the rate of wave V latency change. The main factor for EABR changes was the time in sound. Indeed, significant maturation was observed over the first 2 years of implant use only in the group with early-onset deafness. In this group maturation of wave V progressed as in the ABR model of [Eggermont, J.J., Salamy, A., 1988a. Maturational time-course for the ABR in preterm and full term infants. Hear Res 33, 35–47; Eggermont, J.J., Salamy, A., 1988b. Development of ABR parameters in a preterm and a term born population. Ear Hear 9, 283–9] of normal hearing children: a sum of two decaying exponential functions, one showing an early rapid decrease in latency and the other a slower decrease. Remarkably, the time-constants fell well within the ranges described by Eggermont and Salamy (i.e., 3.9 and 68 weeks), consistent with the time-course of the neurophysiological mechanisms presumably involved in auditory pathway maturation during the first 2 years of life: i.e., myelination and increased synaptic efficacy. In contrast, relatively little change in wave V was evident in children with late-onset deafness. In agreement with the notion that EABR maturation follows an apex-to-base gradient as described for ABR, we observed that wave V latencies were longer for the basal than the apical end of the implant electrode array and remained so throughout the study period, whatever the time of onset of deafness.

☆ Part of the results reported in this paper were presented at the Seventh European Symposium on Paediatric Cochlear Implantation, Geneva, Switzerland, May 2–5, 2004.

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doi:10.1016/j.clinph.2006.11.010

Conclusions: The findings in the early-onset of deafness group support the theory that auditory pathways remain "frozen" during the period of sensory deprivation until cochlear implant rehabilitation restores the normal chronology of maturational processes. In children with late-onset deafness, however, some maturational processes may occur before the onset of deafness, and thus less additional maturation is required during the first two years of implant use resulting in no significant EABR latency changes being observed in this period. The results suggest that the rehabilitation-induced plasticity of the auditory pathways is, in case of late auditory deprivation, unlikely to result in neurophysiological outcomes similar to those observed in children with early auditory deprivation.
Significance: Changes in EABR wave V latency over the first 2 years of cochlear implant use were found to be well fitted by the sum of two decaying exponential functions in children with early-onset deafness. This is in line with the maturation of ABR wave V latency in normal-hearing children over the first two years of life. Further studies are needed to assess whether the differences observed in terms of auditory pathways maturation are associated with consistent differences in terms of language development.

Keywords: Cochlear implant; Auditory brainstem response; Wave V; Modeling; Maturation; Plasticity; Onset of deafness

1. Introduction

Multiple-channel cochlear implants overcome basilar membrane or cochlear hair-cell damage by encoding acoustic information and providing electrical stimulation directly to the auditory nerve. Spectral information is transmitted to the auditory nerve by allocating a frequency range to each stimulation-electrode channel according to the cochlea's tonotopic organization. As a result, high- and low-frequency sounds are conveyed by electrode channels located at, respectively, the basal and apical ends of the cochlear implant electrode array. The stimulation delivered to the auditory nerve is then conveyed through the brainstem auditory pathways much as in acoustic processing in normal-hearing subjects. It is of neurophysiological interest to determine how auditory brainstem developmental plasticity can be promoted by chronic electrical stimulation in children who have never heard before. The comparison of auditory brainstem maturation between hearing children and congenitally deaf children fitted with a cochlear implant may provide some answers to this question. If comparable maturation patterns were found, this would strongly support the idea that auditory brainstem maturation, rather than being definitively determined at birth, is an activity-dependent process that can be equally promoted either by auditory or by electrical input.

Central to this study is the comparison between maturation of electrically evoked auditory brainstem response (EABR) in implanted children and acoustically evoked brainstem responses (ABR) maturation in hearing children. Previous studies have suggested that ABRs continue to follow maturational processes after birth (Hecox and Galambos, 1974; Teas et al., 1982; Krumholz et al., 1985). Specifically, ABR wave I, III and V latencies have been shown to decrease with conceptional age (i.e., age at time of birth plus days of life) (Starr et al., 1977). Accordingly, normative data have been developed for ABR latency as a function of conceptional age, providing indirect markers of auditory nerve and brainstem pathway maturation. For full-term infants, the chronology described by Uziel et al. (1980) suggests that adult latency values will be reached by 2–3 months post-birth for ABR wave I (auditory nerve), by 8–12 months for wave III (lower brainstem) and by 12–24 months for wave V (upper brainstem). This pattern of ABR maturation in hearing children over their first two years of extra-uterine life is now well established. When re-analyzing ABR latency data from the literature, Eggermont (1985a) found that a model utilizing two exponential decay functions provided the best fit (i.e., minimum mean square error) with respect to the ABR maturational time-course. Wave V latency maturation, up to 100 weeks' conceptional age (see Fig. 1), could be well fitted by the sum of 2 decaying functions, with time-constants of 4 and 50 weeks, as follows (Eggermont, 1985a):

$$L_V(t) - L_V(a) = 4494\ \exp(-t/4) + 2.22\ \exp(-t/50)$$

where "t" is the time at which wave V latency is measured and L_V (a) is the adult wave V latency value, taken as equal to 5.60 ms.[1]

This model was sufficiently robust to accurately account for ABR data from various institutions; providing a valid tool for predicting normal ABR latency maturation. Interestingly, the first, most rapidly decaying exponential function was found to fit the early rapid maturation of wave I (the compound action potential of the auditory nerve) for which latency reaches adult values at 45 weeks – i.e.

[1] This model is adapted from the Malthus model of exponential growth applied to a growing mass of bacterial colony or nerve cells:

$$n(t) = n(0)\exp(rt)$$

in which "$n(0)$" is the initial number of elements and "r^{-1}" is the time-constant of the increase. In this model, the term time-constant means that every r^{-1} time unit the number of elements "$n(t)$" increases by a factor of $e = 2.72$.
In the real world, the growth of bacteria or nerve cells encounters a ceiling at "n_{max}" (full-grown or adult state) and the difference between the actual state and this "n_{max}" decreases exponentially as follows:

$$n_{max} - n(t) = n_{max}\exp(-rt).$$

This decaying exponential function, described as the "charging capacitor model", stipulates that every r^{-1} time unit (corresponding to the time-constant of the function), the difference with respect to the full-grown or adult state, decreases by a factor of $e = 2.72$ (for more details, see Eggermont, 1985b).

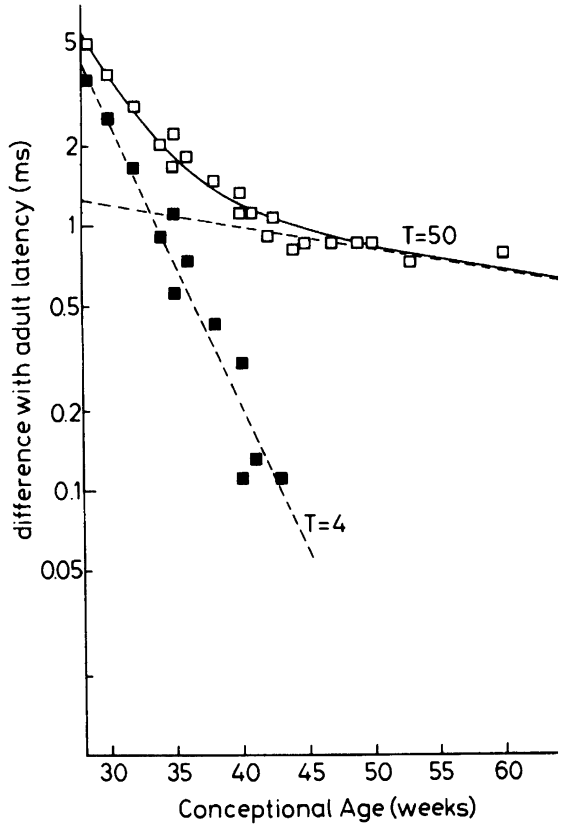

Fig. 1. Modeling of ABR wave V maturation in normal-hearing full-term infants (adapted from Eggermont, 1985a). Data from different institutions were analyzed. To make sure that the observed changes in latency were due to a maturational effect and not biased by any across-institution differences in ABR recording equipment, differences with respect to adult wave V latency (as measured in the same clinic and with the same equipment) are plotted as a function of conceptional age. The maturational time course of wave V latency is well fitted by the sum of two exponential functions with time constants of 4 and 50 weeks respectively. Solid symbols correspond to the early portion of the curve after correction for the contribution of the second exponential function.

slightly after term birth (Eggermont, 1992). The second decaying exponential function, with a slower time-constant, might be interpreted as reflecting the maturation of auditory brainstem structures. The latency difference with respect to adult values for wave V (presumably originating in the lateral lemniscus) was found to become negligible by 3 years of conceptional age. From other ABR studies, it can also be inferred that the developmental maturation of auditory brainstem structures is usually complete by the third year of extra-uterine life (Fria and Doyle, 1984).

It is noteworthy that peripheral maturational processes, rather than cortical ones, may represent the limiting factor for auditory system maturation. Eggermont (1985a, 1988) showed that the maturation of short-, middle- and late-latency auditory evoked potentials could be fitted by a sum of exponential decay functions with unified time-constants for the three auditory evoked potentials. In particular, no differences in latency change rates were found between ABRs and the fast-maturating P2 and N2 cortical potentials. The accepted explanation for this was that the maturation of cortical potentials may depend on maturational changes in brainstem auditory pathways, including myelination processes.

Arguments in favor of activity-dependent central auditory system plasticity were reported for deaf children receiving cochlear implants. Ponton et al. (1996b, 2001) compared the maturation of cortical auditory evoked potentials (in particular, the P1 response – also known as P50, and thought to originate in the primary auditory cortex) in age-matched normal-hearing and cochlear implant children in response to acoustic clicks and biphasic current pulses, respectively. They found that P1 latency in a group of cochlear implantees with a mean sensory deprivation period of 4.5 years reached adult values 5 years later than in the normal-hearing group (15.5 vs 10.5 years of age, respectively). Thus, the chronological pattern of maturation was approximately the same in the cochlear implant group, but with a delay matching the period of auditory deprivation (Ponton et al., 1996a). Accordingly, there remains no difference between young cochlear implantees and their hearing peers when the P1 latency decrease rate is expressed as a function of time in sound (i.e., chronological age minus period of auditory deprivation) and of chronological age, for the two populations, respectively (Eggermont et al., 1997, 2003). In congenitally deaf children, Sharma et al. (2002a,b, 2005) showed that age at implantation significantly determined post-implantation maturation of P1 latency measured in response to speech stimuli. Age-appropriate P1 latency was observed by the 6th month of cochlear implant use for age-at-implantation periods of less than 3.5 years. Finally, the time of onset of deafness is also thought to strongly influence the outcomes of cochlear implantation. Subjects with postlingual onset of deafness are known, indeed, to develop better auditory performance after cochlear implantation than subjects with prelingual deafness (National Institutes of Health Consensus Statement, 1995). Taken together, the above data on sensory deprivation period, age at implantation and time of onset of deafness highlight the role of the time in sound (pre- and post-implantation) as a critical factor for investigating auditory pathways maturation in cochlear implant recipients.

Beyond the well-documented maturation of cortical auditory evoked potentials, only a few studies have pointed out that EABR latencies may likewise change over time after implantation. Repeated measurement of EABR wave latencies in cochlear implant children with congenital deafness has nevertheless led to the conclusion that brainstem auditory pathway conduction velocity can significantly decrease over the period between initial stimulation and at least 1-year's implant use (Gordon et al., 2003, 2006). To our knowledge, potential changes in EABR latencies after implantation have yet to be investigated beyond 1 year of implant use. In addition, very little is known about EABR maturation in children with later onset of deafness.

This distinction is important because those children, as opposed to congenital deaf children, did have some auditory experience before the auditory rehabilitation. In other words, for the same period of cochlear implant use, the actual time in sound of children with late-onset of deafness is longer than that of children with congenital deafness since it also includes part of the pre-auditory rehabilitation period.

The EABR waveform pattern is similar to that of ABRs – but without wave I, which is masked by the electrical stimulus artifact – although the EABR usually appears 1.5–2 ms earlier due to the direct stimulation of spiral ganglion cells by the implant electrodes (Starr and Brackmann, 1979). By analogy with the normal ABR, EABR wave III is thought to be generated in the midbrainstem and EABR wave V in the upper brainstem (van den Honert and Stypulkowski, 1986). In the present study, we focused on wave V since it is the most robust EABR component, obtained on more implant electrodes and for more stimulus intensities than the others (Firszt et al., 2002). Following Eggermont (1988), wave V latency was used as the variable of interest to assess auditory brainstem response maturation in young cochlear implant recipients. We sought to answer the following questions: (1) Does the evolution of EABR wave V latency over the first 2 years of cochlear implant use follow a pattern similar to that seen in ABR of hearing children in the first 2 years of life? (2) To what extent can the time of onset of deafness affect wave V maturation?

In order to address these issues, changes in EABR wave V latency were analyzed for the 2-year period following cochlear implant connection in two distinct groups. The first group consisted of children with early-onset deafness (congenital for most of them) and the second of children with late-onset deafness. Exponential decay models, adapted from the model of Eggermont, were tested in both populations to fit the changes in wave V latency over a two-year period from the time of implant connection. Assuming that exposure to environmental auditory inputs may play an important role in auditory pathway maturation, noticeable differences in latency change should be observed depending on the time of onset of deafness. It was hypothesized that auditory maturational processes were likely to have begun before implantation in children with late-onset deafness, but to have started only after cochlear implant connection in the congenitally deaf children. We predicted little or no maturation of wave V latency in children with late-onset deafness. In children with early-onset deafness, we expected that the decrease in wave V latency observed over the first year of implant use by Gordon et al. (2003, 2006) will continue over the second year. By analogy with the biologically realistic model of ABR maturation described by Eggermont (1985a), we further predicted that maturation of wave V latency in children with early-onset deafness would be fit by the sum of two decaying exponential functions, one reflecting maturational process at the most peripheral level and the other at the level of the brainstem. Our underlying assumption was that the chronological pattern of wave V maturation in this group would resemble that described in normal-hearing children, as it is the case for cortical auditory evoked potentials.

2. Subjects and methods

2.1. Subjects

A total of 55 children (24 girls, 31 boys) participated in the study. All met the following inclusion criteria:

- children with profound deafness;
- receivers of the Nucleus® 24 multichannel cochlear implant (CI24M system), with full insertion of the stimulation electrodes (standard straight electrode array).

There was an important difference between two subgroups of the children regarding the onset of profound deafness. One subgroup consisted of 41 children who had either been born deaf or had developed deafness during the first months of life:

- thirty-six of these children were congenitally deaf: cause of deafness was genetic in 16 cases, of infectious origin in 4 (cytomegalovirus disease: 1 case; rubella: 3 cases), neonatal anoxia in 2, unknown in 14;
- three subjects were not diagnosed as deaf at birth but had developed delayed profound deafness diagnosed around 6 months of age;
- two became deaf during the first months of life following meningitis: both were diagnosed as profoundly deaf (bilateral absence of ABR to 100-dB acoustic stimuli) at the age of 7 months.

These children had undergone cochlear implantation at between 1 year 2 months and 12 years 5 months of age (mean = 3 years 4 months). In addition to this early-onset deafness group, a second subgroup comprised 14 children who had developed deafness after the first year of life. The subjects in this second subgroup ranged in age from 1 year 2 months to 4 years 2 months at the time of onset of deafness with a mean age of 2 years 1 month. Cause of deafness was meningitis in five of these children (mean age at deafness onset = 1 year 11 months), familial in four (mean age at deafness onset = 2 years 1 month), and unknown in five (mean age at deafness onset = 2 years 3 months). In this second subgroup, age at implantation ranged from 2 years to 17 years 4 months (mean = 7 years 4 months).

All the children in this study had worn a conventional hearing aid before undergoing cochlear implantation. Most of them showed significant auditory benefit on audiogram, as assessed by comparison of unaided and aided hearing thresholds, prior to cochlear implantation. Accordingly, the period of auditory deprivation was estimated as the interval between the onset of deafness and

the time at which the child first used conventional amplification. The mean period of auditory deprivation in these terms was 1 year 1 month (min = 1 month; max = 2 years 11 months) in the early-onset deafness group and 7 months (min = 1 month; max = 2 years 10 months) in the late-onset group.

2.2. EABR recordings

EABR data were gathered at the end of the regular cochlear implant fitting sessions. Recordings were made without any sedation, while the child was watching a video. EABRs were recorded between a positive Ag–AgCl electrode placed on the vertex and a negative one positioned on the lobe of the implanted ear. A further electrode attached to the forehead served as ground. Electrical stimuli were generated using the manufacturer's interface device (Dual Processor Interface, Cochlear Corporation, Basel, Switzerland) connected to a computer via a serial port. This system also triggered the evoked-potential measurement device (CA 2000 system, Nicolet Biomedical). EABRs were tested for two stimulation electrodes: one located at the basal end of the implant electrode array (electrode 5), and the other at the apical end (electrode 20). Because the quality of EABR recordings is thought to be better at the apical than at the basal end of the electrode array (Gallégo et al., 1996; Thai-Van et al., 2002), electrode 20 was generally tested first. This was done to optimize the chances of getting valid EABR data, in case fatigue prevented the child undergoing complete examination after a long cochlear implant fitting session.

EABRs were measured in response to monopolar stimulation (biphasic pulse trains of duration = 25 μs/phase) delivered at a rate of 11.4 Hz. The programming set-up used arbitrary units ranging from 1 to 255 Cochlear Corporation programming units (p.u.) (increasing by steps of ≈2% per unit) – i.e., a non-linear progression from ≈10 to 1.750 μA. Responses were filtered with a 150–1500 Hz analog band-pass filter and amplifier sensitivity was set at 100 μV. An analysis time of 10 ms was used, with a sampling rate of 25 kHz. For each EABR trace, the averaging process involved 1000 sweeps.

2.3. Wave V latency measurement

For each session and each test electrode, EABRs were measured at decreasing stimulus intensities. The starting stimulus level corresponded to the upper limit of the appropriate range of electrical stimulation defined during the cochlear implant fitting session. To verify the reproducibility of the EABR peaks obtained, two averages of 1000 sweeps were collected at that level, which usually ranged between 190 and 200 p.u. (i.e., between 469 and 574 μA). The experimenter then decreased the stimulus level by 5 p.u. steps down to the extinction of wave V, which defined the EABR threshold. Fig. 2 shows typical EABR recordings obtained at decreasing stimulus intensities. In agreement with literature data, including previous work by our own team, wave V latency was found to be insensitive to stimulus intensity at high intensities (Gordon et al., 2003; van den Honert and Stypulkowski, 1986; Gallégo et al., 1999), but to increase with decreasing stimulus intensity over the lower half of the cochlear implant's electrical stimulation range, with a noticeable latency increase at the level of the EABR threshold (Firszt et al., 2002; Gallégo et al., 1996; Shallop et al., 1990). Accordingly, so as to avoid any stimulus intensity effect, wave V latency was measured from EABR traces that showed no variation in latency value: i.e., at those stimulus levels at which it remained stable.

2.4. Data analysis

We analyzed changes in EABR wave V latency over the 2 years following cochlear implant connection, in the early- and late-onset of deafness groups. In the early-onset of deafness group, the follow-up started, at the latest, 2 months after cochlear implant connection (day of cochlear implant connection or one week after: 36 subjects; 1 month post-connection: 3 subjects; 2 months post-connection: 2 subjects). In the late-onset deafness group, the follow-up started at the latest 1 week after connection for all subjects. To get a reasonable estimation of individual changes over the 2-year-period, the minimum number of times at which each subject had to be tested was set at 5. Each individual series of measurements included data from 5 or more of the following test times: day of cochlear implant connection, 1 week post-connection, and 1, 3, 6, 9, 12, 18 and 24 months post-connection. Shorter follow-ups were not used in the analysis. Accordingly, individual changes in wave V latency as a function of post-connection time were analyzed in all 55 children for electrode 20 and in 42 children for electrode 5 (i.e., 32 children from the early-onset group, and 10 from the late-onset group). The observed changes were first fitted with a linear model using log-transformed values of wave V latency and time. This allowed the potential effects of test electrode, onset of deafness, age at implantation and duration of sensory deprivation on the modeled latency changes to be tested (the statistical significance level was set at $p < 0.05$). The potential interactions of these effects with the rate of latency change were also tested. Following Eggermont (1985a), biologically realistic fitting models using decaying exponential functions were then tested on the basis of the best fit with respect to minimum mean square error. This was done in order to estimate accurately the EABR maturational time-course as described by maturation time-constants. Statistical analyses were performed with the SAS 8.0 software package (SAS Institute, SAS Campus Drive, Cary, NC). The parameters of the most appropriate decaying exponential model were estimated with SAS's "Proc Mixed"

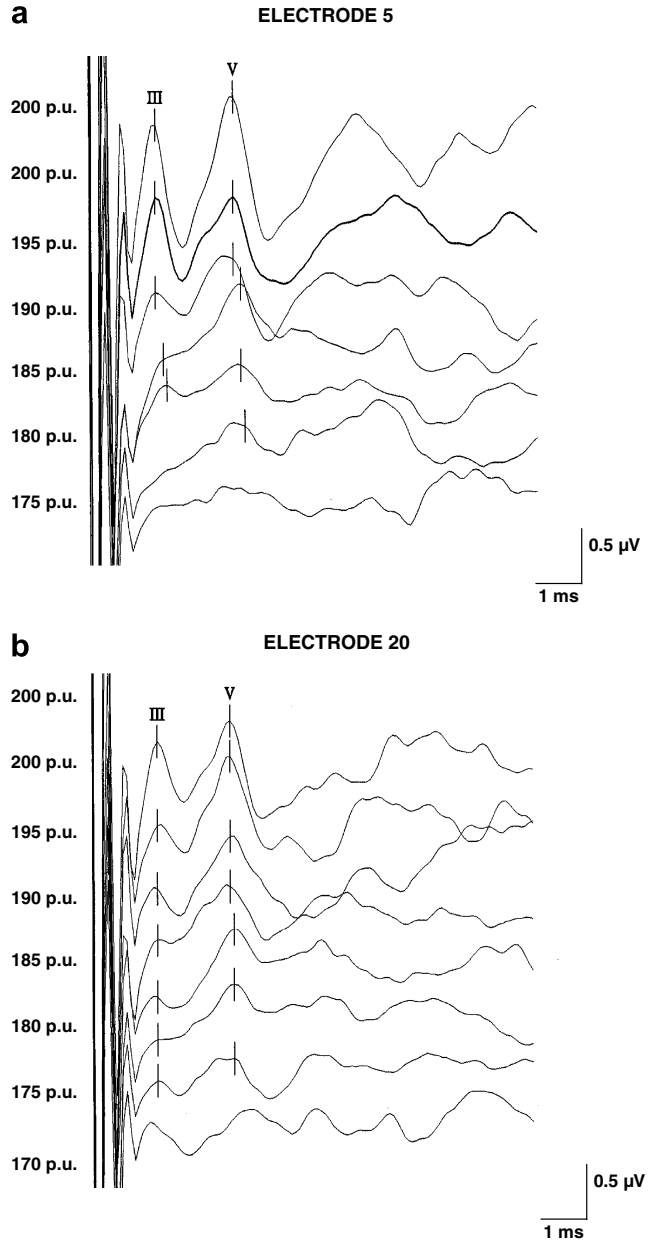

Fig. 2. EABR recordings obtained with decreasing stimulation levels in a 3-year-old girl after 1 year of implant use. The stimulation level is decreased by steps of 5 p.u., from an initial value corresponding to the upper limit of the cochlear implant stimulation range. The typical EABR waveform pattern is similar to that of an ABR – but without wave I, masked by the electrical stimulus artifact, and with waves III and wave V occurring 1.5–2 ms earlier. The EABR threshold corresponds to the lowest stimulation level that still elicits an identifiable wave V response. (a) EABR recordings at the basal end of the cochlear implant electrode array (electrode 5). Note the reproducibility of the EABR peaks for high stimulation levels. The same wave V latency value is found at 200 and 195 p.u. (3.32 ms). The EABR threshold is 180 p.u. (b) EABR recordings at the apical end of the electrode array (electrode 20). Note that stimulus intensity does not affect wave V latency for half of the recordings (top of the figure). The value of wave V latency remains unchanged (3.30 ms) from 200 to 190 p.u.. The EABR threshold is 175 p.u.

and "Proc Nlin" procedures. Nested models were compared with usual F statistics based on residual sums of squares.

3. Results

3.1. Individual changes in EABR wave V latency after cochlear implant connection

Table 1 shows the number of measurements gathered according to test time and electrode in the early- and late-onset deafness groups. A total of 668 EABR wave V latency values were measured in children with early-onset deafness versus 168 in the late-onset group. There was no significant difference in the number of observations between children with early- and late-onset deafness for electrode 5 (heteroscedastic t-test: $t(17) = 0.45$, $p = 0.66$) or electrode 20 (heteroscedastic t-test: $t(24) = 0.34$, $p = 0.74$). On average, wave V latency was found to decrease over time in children with early-onset of deafness for both electrodes 5 and 20, with respective mean starting values of 4.23 and 4.12 ms and mean final values of 3.63 and 3.48 ms. For the same observation period, a very slight decrease in mean latency values was seen in children with late-onset deafness (electrode 5: from 3.99 to 3.82 ms; electrode 20: from 3.83 to 3.65 ms). The decrease in wave V latency, measured for each subject as the difference between the initial and the latest measurement taken, was greater in the early- than in the late-onset deafness group both for electrode 20 (heteroscedastic t-test: $t(33) = 5.77$, $p < 0.00001$) and electrode 5 (heteroscedastic t-test: $t(16) = 4.02$, $p < 0.005$).

Fig. 3 shows individual patterns of wave V latency decrease for the two test groups. Although there was considerable heterogeneity in response level across subjects, a general pattern of EABR wave V maturation emerged in children with early-onset of deafness. These children exhibited a rapid decrease in wave V latency during the first 10 weeks of implant use, followed by a slower decrease. The same pattern of change was seen at both the apical and basal ends of the implant electrode array. Conversely, in all but two subjects with late-onset of deafness, no decrease in wave V latency was observed, irrespective of test electrode.

3.2. Linear model of EABR wave V latency decrease

Using log-transformed values of EABR wave V latency and of time, change over time in wave V latency could be fitted by a decaying linear model as follows:

$$\text{Log(wave V latency)} = a + b\,\text{Log}(t) \quad (1)$$

where "t" is the time at which wave V latency was measured, "a" is the starting wave V latency and "b" is the slope of decrease.

Because of the heterogeneity in response level across subjects, each individual pattern of change had to be modeled taking the subject-specific response level into account. For the ith measure of the jth patient, the above linear model becomes:

$$\text{Log(wave V latency}_{ij}) = a_j + b\,\text{Log}(t_{ij}) + e_{ij}. \quad (2)$$

with $a_j = a + u_j$.

The term "u_j" represents the deviation between the average response of the jth patient and the overall average ("a"), and the term "e_{ij}" represents the residual error.

When integrating other covariates than time into the model, it turned out that latency values were influenced by neither age at implantation ($p = 0.87$) nor duration of auditory deprivation ($p = 0.73$). The slopes of decrease, however, did differ significantly according to the onset of deafness ($t = 5.73$; $p < 0.0001$). Using a double logarithmic scale, the slope of decrease was $-0.04 \pm \text{SEM} = 0.001$ ($t = -31.26$; $p < 0.0001$) in children with early-onset deafness and $-0.01 \pm \text{SEM} = 0.002$ ($t = -5.10$; $p < 0.0001$) in children with late-onset. Conversely, no interaction was found between slope of decrease and age at implantation ($p = 0.22$), indicating that age at implantation did not influence the rate of latency change. When splitting children with early-onset deafness into two subgroups depending on whether deafness was congenital or not, no difference in rate of maturation could be demonstrated between the five subjects who had developed deafness around 6–7 months of age and those who were born deaf ($p = 0.68$).

The starting wave V latency, measured on the day of cochlear implant connection, was found to be longer in the early- compared to the late-onset group ($p < 0.0001$), with a difference of 9%. In addition, starting wave V latency was longer for electrode 5 than for electrode 20, with a difference of 4% ($t = 12.23$; $p < 0.0001$). There was, however, no interaction between slope of decrease and test electrode ($p = 0.10$): i.e., no difference in rate of maturation could be observed between the basal and the apical ends of the implant electrode array. Indeed, the final wave V latency was still longer for electrode 5 than electrode 20 ($p < 0.0001$).

3.3. Fitting models using decaying exponential functions

As well as log-transforming the original data to build a linear model, it was also possible to fit the original data with a decaying exponential model, adapted from the Malthus model of exponential growth, as follows:

$$\text{Wave V latency}(t) = A + \alpha \exp(-t/T) \quad (3)$$

where "t" is the time at which wave V latency was measured, "A" is the asymptotic wave V latency value, and "T" is the latency change time-constant. According to this model:

- for $t \to \infty$, wave V latency tends towards the asymptotic value "A"
- the starting value of wave V latency (for $t = 0$) is equal to $A + \alpha$.

However, using only one exponential to fit the data did not take into account the initial rapid decrease in wave V latency, observed in children with early-onset of deafness. In addition, differences relative to time of onset of deafness and test electrode had also to be taken into account. When fitting the early-onset group latency data with respect to minimum mean square error, the above exponential model became:

$$\text{Wave V latency}(t) = 3.36 + [0.29 \exp(-t/T_0) + 0.55 \times \exp(-t/T_1)] + \text{c.electrode} \quad (4)$$

where $T_0 = 3.9$ weeks, $T_1 = 68$ weeks, and $c = 0.12$ ms.

This means that changes in wave V latency could be modeled as the sum of two decaying exponential functions with respective time-constants of 3.9 weeks (T_0) and 68 weeks (T_1). The model thus allowed for the initial rapid decrease in latency values followed by a slower decrease. Electrode 20 served as reference in Eq. (4). The starting latency value (corresponding to $t = 0$) was estimated as $3.36 + 0.29 + 0.55 = 4.20$ ms for electrode 20, and $4.20 + \text{c} = 4.32$ ms for electrode 5.

The pattern of latency change differed clearly in the late-onset group, and was described as follows:

$$\text{Wave V latency}(t) = 3.36 + [0.20 \exp(-t/T_2) + 0.27 \times \exp(-t/T_3)] + \text{c.electrode} \quad (5)$$

where $T_2 = 47$ weeks, $T_3 \to \infty$, and $c = 0.12$ ms.

Table 1
Mean wave V latency values (ms) according to subjects group (early- or late-onset of deafness), test electrode and time post-connection

Time post-connection	Early-onset deafness				Late-onset deafness			
	Electrode 5		Electrode 20		Electrode 5		Electrode 20	
	N	Mean	*N*	Mean	*N*	Mean	*N*	Mean
1st day	7	4.23	15	4.12	6	3.99	7	3.83
1st week	21	4.21	30	4.09	6	3.87	11	3.84
1 month	25	4.07	36	4.02	8	3.92	11	3.84
3 months	30	3.97	37	3.83	8	3.88	12	3.84
6 months	28	3.91	39	3.75	8	3.92	13	3.82
9 months	24	3.84	27	3.68	7	3.75	11	3.75
1 year	24	3.75	29	3.60	10	3.81	13	3.67
18 months	28	3.70	38	3.57	7	3.77	11	3.75
2 years	25	3.63	37	3.48	8	3.82	11	3.65

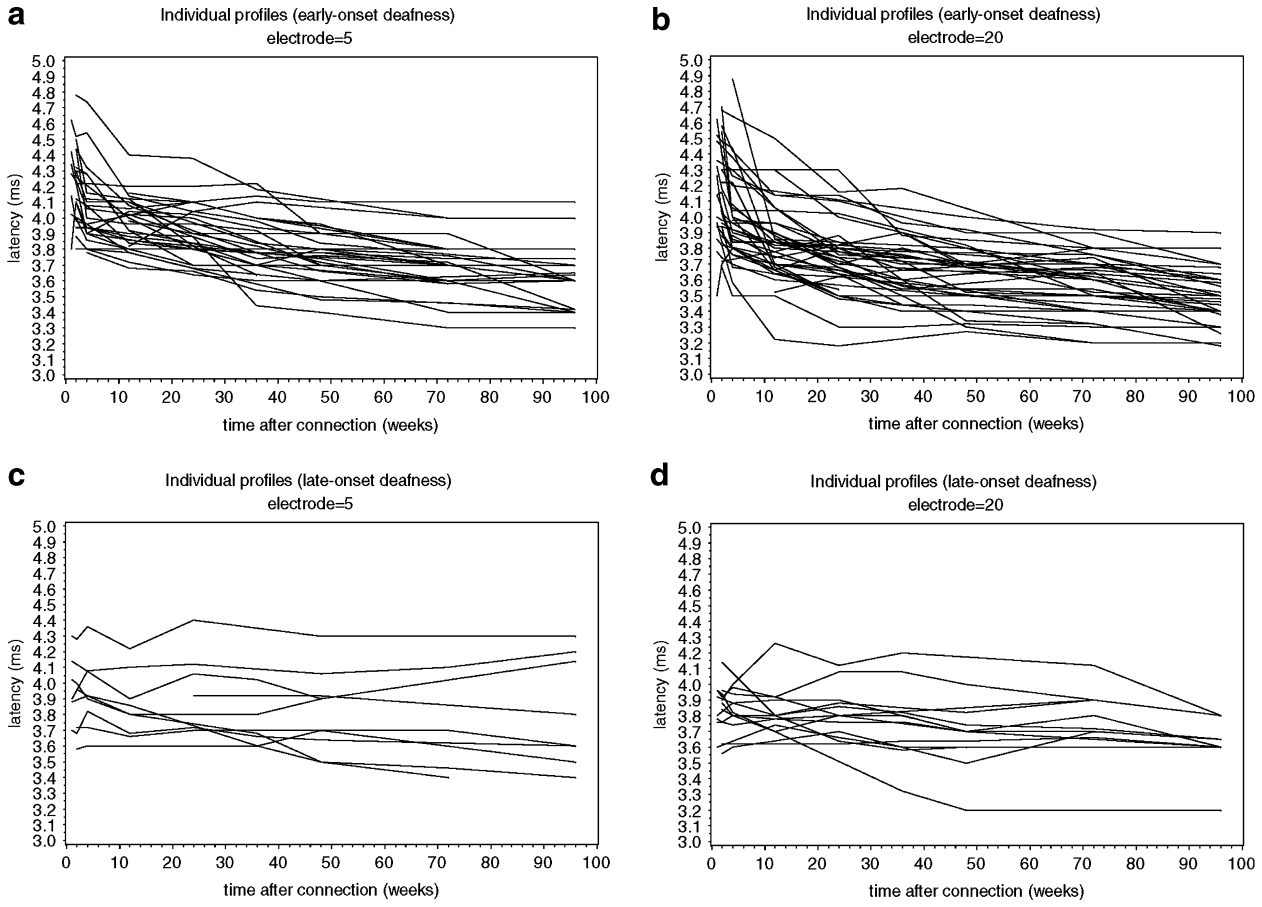

Fig. 3. Individual patterns of decrease in wave V latency for the two test groups. Individual changes in wave V latency are shown for electrodes 5 and 20 in children with early-onset deafness (diagrams 3a and 3b), and with late-onset deafness (diagrams 3c and 3d). Note the absence of latency maturation in all but two subjects in the late-onset deafness group.

The starting latency value was estimated as $3.36 + 0.20 + 0.27 = 3.83$ ms for electrode 20 (which served as reference), and $3.83 + c = 3.95$ ms for electrode 5. In contrast with the modeling results for the early-onset group, the values of the time-constants (with $T_3 \to \infty$) did not allow any noticeable maturational process to be modeled over the studied period. Fig. 4a and b illustrate the modeling of latency changes, with lines of best fit and 95% confidence intervals around the mean latency value, in the two test groups for electrodes 5 and 20, respectively. The final latency values, as predicted by the double exponential model, are shown in Table 2. Comparison of goodness-of-fit between the simple exponential model [Eq. (3)] and the double exponential model [Eqs. (4), and (5)] confirmed that the double exponential model provided a better fit (F statistics based on residual sums of squares, $p = 0.03$).

4. Discussion

4.1. Conditions and time-course of auditory brainstem maturation in children receiving a cochlear implant

The present study assessed potential EABR maturation in two groups of cochlear-implanted children with different hearing-loss onset times: children with early (mostly congenital) onset of deafness and children with late-onset (after 1 year) deafness. We proposed a predictive model of EABR wave V latency change over the 2-year period following cochlear implant connection. The modeling of changes in EABR wave V latency with time was based on mean values of each of the two groups, allowing the rates of EABR maturation to be compared. Little or no wave V latency maturation occurred in children with late-onset deafness (with two exceptions), while strong maturation was observed in the early-onset group. This maturation could be mathematically fitted by a biologically realistic model, described as the sum of two decaying exponential functions, one showing an early rapid decrease in wave V latency and the other a slower decrease.

Using repeated electrophysiological measurements in cochlear implant children with early-onset of deafness, Gordon et al. (2003, 2006) were the first to demonstrate a shortening of EABR wave III and V latencies and a decrease in neural conduction times in the lower and upper brainstem throughout the first year of implant use. Here we focused on modeling changes in EABR wave V latency (i.e., neural conduction in the upper brainstem) occurring during the initial 2 years of implant use. The 2-year evaluation is necessary for a more complete comparison with hearing

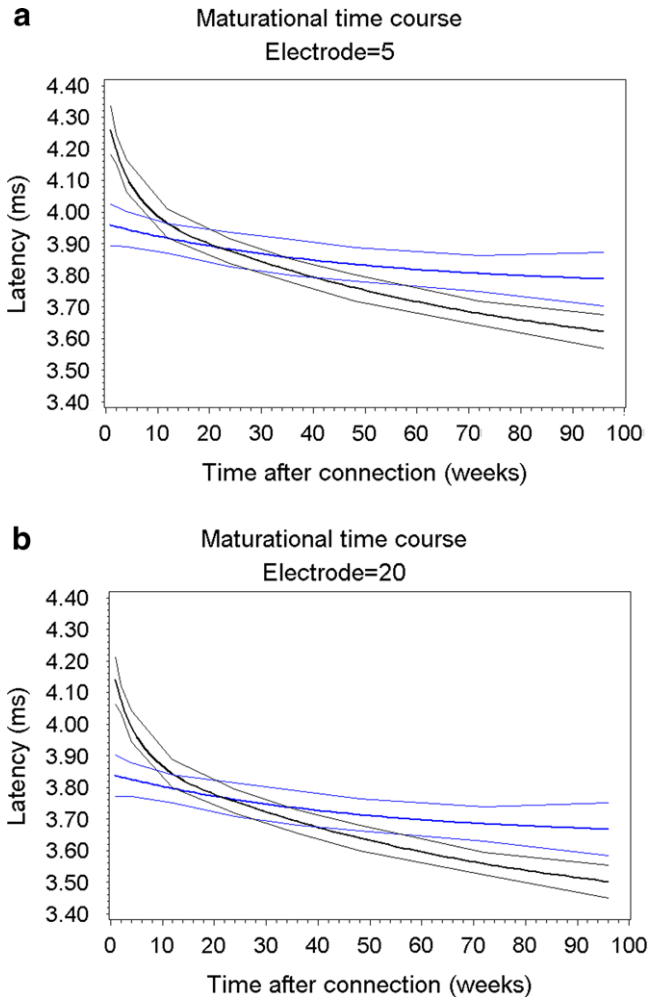

Fig. 4. Decaying exponential model of wave V latency changes for electrodes 5 (a) and 20 (b). The lines of best fit (bold lines), with confidence limits at the 95% interval, are shown in black for the early-onset deafness group and blue for the late-onset deafness group. In the early-onset deafness group, the maturational time-course follows an exponential decrease with an initial rapid decrease in latency values during the first 10–11 weeks of implant use followed by a slower decrease. In contrast, no exponential decrease in latency values can be observed in the late-onset deafness group, whatever the test electrode.

children where ABR maturation typically ends at roughly 2 years of age (Eggermont, 1992; Eggermont and Ponton, 2003; Fria and Doyle, 1984). The wave V latency values predicted by our modeling at 2 years were shorter than those predicted by Gordon et al. (2002, 2003, 2006) for children with 1 year of implant use (>4 ms at basal electrode 3) though in line with the values reported in adults by our group (Gallégo et al., 1996, 1997, 1998) and by other researchers (e.g., 3.69 ± 0.14 ms at the apical end of the array and 3.76 ± 0.20 ms at the basal end (Firszt et al., 2002)). It is possible that the decrease in EABR wave V latency may reflect not only maturation of the upper auditory brainstem per se, but also maturational changes affecting the lower auditory brainstem (EABR wave III) or even the responses of the auditory nerve to electrical stimulation (i.e., the electrical compound action potential (ECAP N1 wave) and EABR wave II). However, our model of EABR wave V latency changes is in line with previous research on EABR including an analysis of peripheral components and interwave latency changes. Analyzing EABR measurements taken at 0, 2, 6 and 12 months after connection, Gordon et al. (2006) found wave V latency decreases at all test sessions. However, significant changes in latency were found only within the first weeks of implant use for ECAP N1 and interwave N1–III, the first 2 months for wave III, and the first 6 months for interwave III–V. Taken together, the temporal patterns of maturation of wave III, V and interwave III–V suggested that the observed decrease in interval III–V was, at least from 2 to 6 months, produced by a shortening in wave V latency. Gordon et al. (2006) reported much smaller latency changes for EABR early waves (ECAP N1, EABR wave II) and interwaves (N1–II, N1–III) than for EABR wave V, and showed that these changes could not be well modeled by a decaying exponential curve. Thus, changes in latency that may occur at the level of the auditory nerve and/or the caudal portion of the brainstem are unlikely to underlie those observed for EABR wave V, particularly from the 3rd month of implant use on. Here, the early rapid decrease in wave V latency, possibly the result of a peripheral maturational process as discussed in the next section, was found to take place within the first 10 weeks of implant use. Another possible influence on EABR wave V latency changes would be changes in the environment of the implant array after cochlear implantation. Such changes may lead to electrode impedance variations that could, in turn, affect EABR measurements. However, these variations are now well known, and electrode impedance has been reported to stabilize as soon as 1–3 months post-connection (Henkin et al., 2003, 2005).

4.2. Comparison of developmental plasticity of the auditory brainstem in normal-hearing children and children with cochlear implants

Eggermont (1988) showed that the maturation of sensory evoked-potential latencies can be well fitted using the sum of

Table 2
Wave V latency values (ms) at 96 weeks post-connection, as estimated by the decaying exponential model, according to subjects group (early- or late-onset of deafness) and test electrode

Early-onset deafness				Late-onset deafness			
Electrode 5		Electrode 20		Electrode 5		Electrode 20	
Average	95% confidence interval	Average	95% confidence interval	Average	95% confidence interval	Average	95% confidence interval
3.62	3.57–3.68	3.50	3.45–3.55	3.79	3.70–3.87	3.67	3.58–3.75

decaying exponential functions, irrespective of sensory modality (auditory, somatosensory or visual). Moreover, he demonstrated that the pattern of latency decrease can be unified for auditory, somatosensory and visual evoked potentials. In all examined cases, decreases in latency could indeed be described as a combination of fast and slow processes with respective time-constants around 4 and 50 weeks (Eggermont and Salamy, 1988a). For acoustically evoked ABRs in normal-hearing children, the short time-constant process is completed shortly after birth (from 40 to 45 weeks' conceptional age), while the slower time-constant process reaches adult latency values by 3 years' conceptional age (Eggermont, 1992). Eggermont (1985a) interpreted the first rapid time-constant as reflecting the maturation of ABR wave I, in agreement with the notion that auditory pathway maturation follows a centripetal pattern from the auditory nerve towards central auditory neurons. In addition, he found that the slower time-constant was independent of latency range, being common not only to ABR waves III and V, but also to the P2 and N2 auditory evoked potentials of cortical origin (Eggermont, 1988). The present study provides several keys to understanding developmental plasticity in children who use a cochlear implant.

Our main result is that the EABR wave V latency decrease can, in children with early-onset deafness, be fitted using a model similar to that proposed by Eggermont (1988) for ABR maturation. This suggests that auditory pathway maturation may be promoted by acoustic or electrical auditory input in the same way. Comparing ABR maturation in preterm and full-term infants, Eggermont and Salamy (1988b) observed that earlier exposure to environmental sounds had no positive effect on maturation in preterms, nor did prematurity delay their maturation. From that result, it may be inferred that ABR maturation will probably be governed by genetically transmitted or innate maturational processes with negligible influence of experience. However, we have here demonstrated that auditory pathway maturation may, at least in part, be mediated by activity-dependent processes. Indeed, the EABR latency decrease we observed in children with early-onset deafness could not be explained by inherited or innate hearing abilities. In these children, the observation of an initial rapid decrease in latency, followed by a slower one, is consistent with the theory of a centripetal maturation beginning at the level of the auditory nerve then reaching the upper brainstem, as proposed for ABR by Eggermont (1992). This is supported by the fact that the time-constants of both the initial rapid decrease and the subsequent slower process fell in the same ranges as described for ABR maturation (respectively, 3.9 and 68 weeks). It is of particular interest that Eggermont, in his model of ABR wave V maturation, has attributed the first decaying exponential function to the early rapid maturation of the compound action potential of the auditory nerve and the second to brainstem maturation. In our double exponential model of EABR wave V maturation, a possible interpretation would be that the first decaying exponential function may also account for rapid maturational changes occurring at a peripheral level while the second may directly reflect the maturation of the brainstem generators of wave V.

Utilizing a new approach to modeling auditory EABR wave V latency maturation, we also tested for potential differences in the time-course of latency data between stimulation electrodes located at the basal and apical ends of the implant array. The linear modeling of the data did not show any difference in the rate of latency change. However, the starting wave V latency was significantly longer for electrode 5 than for electrode 20 in all children, suggesting that the chronology of maturation was not the same between basal and apical electrodes. This is in agreement with previous results from our team, pointing out the immaturity of the basal part of the human cochlea in preterm neonates (Collet et al., 1987; Soares et al., 1988). It is commonly held that the spatial encoding of frequency along the human cochlea matures during development, with low-pitched sounds being represented first (Rubel and Ryals, 1983). In the light of these physiological data, it is not surprising that longer EABR latency values have been found for the basal than for the apical end of the implant electrode array, both at the beginning and the end of the study period. In children with late-onset deafness, some intra-cochlear maturational processes may occur prior to the onset of deafness, leading to a tonotopic organization of the cochlea similar to that found in hearing children of the same age; that longer latency values are predicted for the basal electrode at the end of the study period is consistent with previous reports of a gradual EABR latency decrease from base to apex in adult cochlear implant recipients (Firszt et al., 2002; Gallégo et al., 1996; Miller et al., 1993; Shallop et al., 1990). One question raised is why children with early-onset deafness would also exhibit longer starting latency values for basal than for apical electrodes. It should be borne in mind that these subjects, because of the degree of their hearing impairment and the early-onset of their deafness, were unlikely to have ever experienced high-pitched sounds before implantation, whereas they may have had some residual low-pitched perception (Thai-Van et al., 2001, 2004). Such a lack of hearing perception might interfere with the development of frequency representation along the basilar membrane, in particular for high-pitched sounds. Accordingly, our decaying exponential model predicts in the early-onset deafness group not only longer starting latency values for the high- than for the low-frequency electrode, but also longer starting latency values compared to the late-onset group whatever the test electrode.

4.3. Influence of onset of deafness, age at implantation and sensory deprivation period on auditory brainstem plasticity: potential clinical implications

An important issue is that of the relation between auditory pathway maturation in young cochlear implantees and

their pre- and post-implantation time in sound. It is commonly accepted that age at onset of deafness, age at implantation, and duration of auditory deprivation affect to a great extent the auditory performance after cochlear implantation, as opposed to etiology of deafness (National Institutes of Health Consensus Statement, 1995). While the congenital or meningitic origin of the deafness does not seem to have much influence on post-implantation auditory performance, children who have the chance to develop an auditory memory before the implantation tend to demonstrate better performance than those who are born profoundly deaf (Gantz et al., 1994). That is, the longer the pre-implantation time in sound, the better the outcomes of cochlear implantation. The role of age at implantation has been supported by research on the linguistic impact of cochlear implantation in deaf children. Congenitally deaf children having had cochlear implantation before 2 years of age have been found to show generally better expressive and receptive language development than those implanted later (Svirsky et al., 2004). It has been demonstrated that the duration of auditory deprivation may influence EABR characteristics. We recently had the opportunity to study EABR in patients equipped with a newly designed bilateral cochlear implant made of two electrode arrays placed bilaterally inside the scala tympani and controlled by a single processor (Thai-Van et al., 2002). These patients were selected for asymmetry between the two ears with respect to the duration of deafness prior to the implantation, and thus provided an interesting model for in vivo study of the deleterious effect of long-term profound deafness. Repeated EABR measurements from electrodes with symmetric intra-cochlear locations showed that, whatever the pair of electrodes tested and whatever the test time, EABR characteristics varied between the two ears, in a manner dependent on deafness duration. In particular, wave V latency was delayed in the ear with the longer duration of deafness. This strengthens the hypothesis that auditory deprivation adversely affects neural transmission along brainstem auditory pathways.

In the present study, neither age at implantation nor duration of auditory deprivation was found to influence changes of EABR wave V latency over the 2-year follow-up. As opposed to cortical auditory evoked potentials and middle latency auditory response maturation (Ponton et al., 1996b ; Sharma et al., 2002a, 2005; Gordon et al., 2005), EABR maturation is thought to be insensitive to age at implantation. It has been reported that the age at which a child receives the cochlear implant influences neither initial EABR latency and amplitude values nor how they change over time with implant use (Gordon et al., 2003). Our results are in line with those of Gordon et al. (2006) who, analyzing a cohort of children implanted between 12 months and 17 years of age, did not find any influence of the age at the time of testing on the EABR interwave latencies measured at initial activation and half a year after. Here we also found that age at implantation did not influence the rate of wave V latency change, thus was not a limiting factor for auditory brainstem responses plasticity. Because the follow-up started 1 week after connection in most of the participants, chronological age at first testing was not found to be influential either. The fact that there was no influence of the duration of auditory deprivation was more surprising given the results we previously obtained in implanted patients with asymmetric duration of deafness (Thai-Van et al., 2002). Importantly, we controlled for possible pre-implantation auditory input due to the use of a conventional hearing aid and yet found that the time-span between deafness onset and first use of amplification had no influence on latency values. It is arguable that certain demographic characteristics of our population prevented a deprivation effect being disclosed. A possible bias in the present study might be that both the early- and late-onset deafness children had relatively short and homogeneous periods of auditory deprivation (i.e., time-spans between deafness onset and first use of amplification). For a wider range of deprivation periods, some time-dependent constraints on EABR maturation might become more apparent.

The critical role played by the onset of deafness in the present study merits discussion. Although all children in the present study were diagnosed with prelingual deafness (defined as occurring before 5 years of age), the onset of deafness clearly differed between the two tested groups. One may argue that children in the late-onset deafness group (mean age at onset of deafness = 2 years 1 month) might have a developing/mature auditory system at the time they became deaf. Thus it might not even make sense to test for EABR latency changes in this group. However, there is compelling evidence in the literature that neuroplastic changes can occur in the mature mammalian auditory brainstem either under the influence of auditory training (Russo et al., 2005) or chronic intra-cochlear stimulation (Illing, 2001). Moore and colleagues (2002) have shown that chronic intra-cochlear electrical stimulation in adult deafened cats can induce tonotopic reorganization at the level of the inferior colliculus. Given this result, the question remains why EABR maturation was more limited in children with late-onset deafness compared to those with early-onset deafness. Some data in the literature bridge the gap between EABR characteristics and clinical cochlear implant outcomes, which, as mentioned above, are thought to be limited by the onset of deafness. The latency of EABR wave V has been shown to correlate negatively with phoneme recognition scores, at least in adult cochlear implant recipients (Gallégo et al., 1998). That is, the shorter the wave V latency, the better the speech perception skills. Children with late-onset of deafness are likely to develop some speech perception skills before becoming deaf, while children who are born deaf are unlikely to start developing comparable skills prior to auditory rehabilitation. Assuming that a decrease in wave V latency is associated with an improvement in speech perception, a significant decrease in wave V latency is more likely to occur in children with early- than late-onset of deafness

since the former need, as a minimal requirement, to catch up with the speech perception skills of the latter. In a meta-analysis of pediatric cochlear implant literature, poorer speech perception scores have been found in children with congenital than acquired deafness until 1 year post-implant connection, although the difference tends to reverse over time with better speech perception in children with congenital than acquired deafness children after 2–3 years of implant use (Cheng et al., 1999). This suggests that it takes at least one year for congenitally deafened children to overtake those who have achieved some degree of linguistic maturation before becoming deaf. One possible interpretation of our results would be that the remarkable decrease in wave V latency with time in sound observed in children with early-onset deafness may underlie their progress in speech perception. It is reasonable to assume that the speech perception skills of these children would still lag behind those of children with late-onset deafness in the absence of any EABR maturation.

Ponton et al. (1999) developed a theory for the activity-dependent maturation of the auditory system after long periods of deafness. They proposed that the auditory pathways remain minimally plastic during the period of sensory deprivation, until auditory input provided by the implant restores the normal chronology of maturational processes. Our results in the early-onset deafness group are in total agreement with this theory, in that the chronological pattern of EABR maturation between implant connection and 2 years resembled that described for ABR maturation over the first 2 years of life in normal-hearing children. Recent research on middle latency auditory response maturation in cochlear implant children also highlights the plasticity of the auditory thalamocortical pathways after a period of auditory deprivation (Gordon et al., 2005). A possible explanation for the absence of EABR maturation in children with late-onset deafness would be that brainstem auditory pathways had reached a significant degree of maturity by the onset of deafness, and then maintained this degree of maturity during the period of deafness. In support of this, near-mature starting wave-V latencies were predicted by the decaying exponential model in the late-onset deafness group (3.83 and 3.95 ms for electrodes 20 and 5, respectively, versus 4.20 and 4.32 ms in the early-onset deafness group).

4.4. Mechanisms possibly involved in auditory brainstem plasticity in children receiving a cochlear implant

The potential mechanisms underlying EABR maturation in children with cochlear implants can be discussed with regard to those presumably involved in ABR maturation. Well-formed myelin sheaths are observed surrounding the proximal end of the auditory nerve as early as the 26th gestational week – a time at which ABRs can be first recorded (Moore and Linthicum, 2001). At the end of gestation, myelin of mature appearance is normally visible along the auditory nerve central to the glial junction, trapezoid body, lateral lemniscus and inferior colliculus (Gilles et al., 1976). The myelination process is not, however, completed before 1 year of postnatal age in normal-hearing children (Moore et al., 1995). Importantly, the myelination of the auditory brainstem is thought to proceed in parallel with the ABR latency decrease observed during the infantile period (Inagaki et al., 1987). In autopsied infants, specific myelination time-spans have been identified during which the myelinating auditory brainstem structures are liable to be damaged, up to at least 2 years of postnatal age (Kinney et al., 1988). An alternative explanation for ABR maturation in normal-hearing children is in terms of changes in the number and efficacy of synapses. An initial phase of rapid synaptogenesis was described in the central auditory system, concomitant to the myelination processes, leading to maximal synaptic density in the Heschl's gyrus at 3 months of postnatal age, followed by a longer phase of synapse elimination up to 12 years of age (Huttenlocher and Dabholkar, 1997). Since both myelination and changes in synaptic density follow a two-step process, both might explain ABR maturation as modeled by Eggermont (1985a). The short time-constant ABR latency change was interpreted as reflecting the rapid myelination and synaptogenesis processes which both occur perinatally and terminate slightly after term birth, while the slower time-constant was thought to correspond to later processes of myelination and synaptic enhancement (Eggermont and Salamy, 1988a).

Recently, it has been shown that cochlear implants in congenitally deaf cats can restore normal-like anatomy at the endbulbs of Held, the synapses made by auditory nerve fibers onto bushy cells in the anteroventral cochlear nucleus and thought to be involved in sound localization (Ryugo et al., 2005). The fact that the maturational time-course of EABR wave V matches the chronology described for ABR suggests that the two physiological mechanisms presumably involved in normal auditory brainstem maturation may underlie EABR maturation. Is one mechanism more likely to be involved than the other? Ponton et al. (1996c) have made a distinction between the maturation of the different segments of the brainstem auditory pathway corresponding to whether these segments represent asynaptic (intervals I–II and III–IV) or mono-synaptic (intervals II–III and IV–V) pathway. In hearing children, the fact that the interval III–IV, assumed to reflect only axonal conduction, remains constant after birth suggests that increasing conduction velocity due to myelination totally compensates for increasing brainstem auditory pathway length from birth until age 1 (Moore et al., 1995) and possibly age 3 (Moore et al., 1996). The postnatal decrease in ABR interval III–V, conversely, is likely to reflect active synaptic changes affecting the segment IV–V. However, this does not preclude, in children with cochlear implant, the role of myelination as a possible mechanism of EABR maturation. Most children, indeed, have been implanted after age 2 and near-mature auditory pathway length could have been reached before implantation. In this context, the

net effect of any potential myelination process would be a decrease in EABR wave V latency yet. Therefore, a reasonable assumption is that both auditory brainstem myelination and synaptic processes can be induced to resume in deaf subjects by cochlear implant use. Our results are in agreement with the notion that profound deafness in children "freezes" the auditory pathways in a state that depends on the onset of deafness (Eggermont et al., 1997; Ponton et al., 1999). In children with early-onset deafness, the "frozen" state is immature and stimulation with the implant will first cause the very early stages of maturational processes (including the initial phase of rapid synaptogenesis and myelination) to resume. The same physiological processes as in hearing children may then occur, though delayed by the period of sensory deprivation. In children with late-onset of deafness, these physiological processes may, at least in part, have taken place before the onset of profound deafness. Although plastic changes, such as increased synchrony across auditory nerve fibers, cannot be excluded (Gordon et al., 2003; Thai-Van et al., 2004), the net effect of implant use in terms of improved neural conduction time would tend to be much less marked than in congenitally deaf children. The predictions of our decaying exponential model cannot, however, be totally explained by the "freezing-thaw" theory described above. While children in the late-onset deafness group presented initially with near-mature starting wave V latencies, it is somewhat striking that they presented at the end of the follow-up with longer latencies compared to children in the early-onset deafness group. This suggests that the rehabilitation-induced plasticity of the auditory pathways is, in case of late auditory deprivation, unlikely to result in neurophysiological outcomes similar to those observed in children with early auditory deprivation. A possible explanation would be that only children with early auditory deprivation are liable to undergo significant processes of myelination and/or synaptic changes after cochlear implantation.

5. Conclusions

We proposed a statistical model that allows, on the one hand, the prediction of EABR wave V latency changes over the 2 years post-implant connection and, on the other hand, a comparison between children with late- and early-onset of deafness. In the latter, maturation of EABR wave V latency was found to follow the same chronological pattern as that described for ABR wave V in normal-hearing children. The findings agree with the theory of centripetal maturation from the auditory nerve towards central auditory neurons. Further, observed differences between electrode 5 and electrode 20 recordings are consistent with the notion that sound processing takes longer to mature for high- than for low-pitched sound. In addition to providing decisive arguments in favor of rehabilitation-induced plasticity in cochlear-implanted children, the present study indicates that the effect of resuming auditory input may differ greatly depending on the condition of the auditory pathways at the time of deafness onset. Further research is required to assess whether the differences we observed in terms of auditory pathway maturation are associated with consistent differences in terms of language development.

Acknowledgements

Fig. 1 in this article is adapted from Eggermont JJ. Physiology of the developing auditory system. In: Trehub SE, Schneider B, editors. Auditory development in infancy: Plenum Press. New York: 1985 (Fig. 10, page 37), with kind permission of Jos Eggermont and of Springer Science and Business Media. The authors wish to thank Jos Eggermont and Charles Limb for their constructive comments on an earlier version of this manuscript. They are grateful to Tiphaine Bigeard, Véronique Desreux and Muriel Kreiss for their assistance with data collection. The statistical analysis was partially funded by an unrestricted grant from Cochlear AG.

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