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The influence of a sensitive period on central auditory development in children with unilateral and bilateral cochlear implants

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Abstract

We examined the longitudinal development of the cortical auditory evoked potential (CAEP) in 21 children who were fitted with unilateral cochlear implants and in two children who were fitted with bilateral cochlear implants either before age 3.5 years or after age 7 years. The age cut-offs (<3.5 years for early-implanted and >7 years for late-implanted) were based on the sensitive period for central auditory development described in [Ear Hear. 23 (6), 532.] Our results showed a fundamentally different pattern of development of CAEP morphology and P1 cortical response latency for early- and late-implanted children. Early-implanted children and one child who received bilateral implants by age 3.5 years showed rapid development in CAEP waveform morphology and P1 latency. Late-implanted children showed aberrant waveform morphology and significantly slower decreases in P1 latency postimplantation. In the case of a child who received his first implant by age 3.5 years and his second implant after age 7 years, CAEP responses elicited by the second implant were similar to late-implanted children. Our results are consistent with animal models of central auditory development after implantation and confirm the presence of a relatively brief sensitive period for central auditory development in young children.

1. Introduction

The human cochlea is functional at birth (Granier-Deferre et al., 1985; Rubel, 1985), but the auditory system is still immature and undergoes many developmental changes postnatally. This postnatal development is reflected in age-related changes in cortical evoked potentials. For example, the cortical P1 response, which is generated by auditory thalamic and cortical sources, systematically decreases in latency with increasing age (Sharma et al., 1997; Cunningham et al., 2000; Ponton et al., 2000).

Because P1 latency changes with age, P1 latency has been used as an index of maturation of the auditory pathway in populations with abnormal auditory experience (Ponton et al., 1996a,b, 1999; Ponton and Eggermont, 2001; Sharma et al., 2002a,b,c). Sharma et al. (2002c) compared the P1 latencies of 97 congenitally deaf children fitted with cochlear implants with the 95% confidence intervals for P1 latencies derived from age-matched, normal-hearing children. Prelingually deaf children implanted under 3.5 years of age had age-appropriate P1 latencies within 6 months following the

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onset of stimulation. In contrast, the P1 latencies of children implanted after age 7 were delayed relative to normal-hearing controls even after years of stimulation. Sharma et al. (2002c) concluded that the central auditory system is highly plastic for a sensitive period of 3.5 years in early childhood.

While it is likely that there is more than one sensitive period in the central auditory system (Lee et al., 2001; Eggermont and Ponton, 2003; Mostafapour et al., 2002; Gordon et al., 2003) the duration of the sensitive period described by Sharma et al. (2002c) coincides with several developmental changes at the structural level of the auditory cortex. During the first 2–4 postnatal years a massive reorganization of dendritic trees in the cerebral cortex occurs (Conel, 1939; Moore, 2004). Over the first two years, there is a steep increase in the complexity of the branching pattern of the dendritic trees. The complexity decreases in subsequent years. Studies of synaptic densities support this concept by showing an increase in densities during the first year of life ('synaptogenesis'), a peak in synaptic densities between 2 and 4 years ("synaptic overshoot"), and a subsequent slow decrease in synaptic densities to approximately 50% of the peak numbers in adolescent brains (Huttenlocher and Dabholkar, 1997). From the temporal correspondence of these synaptic changes with the sensitive period demonstrated by Sharma et al. (2002c) we can assume that these changes are a significant factor in the etiology of the sensitive period. Other developmental changes continue beyond the duration of the sensitive period, e.g., myelination (Yakovlev, 1967; Paus et al., 1999) and development of neurofilament structure (Moore and Guan, 2001; Moore, 2002), and are less likely to play a major role in the etiology of this sensitive period.

If there is a brief sensitive period for central auditory system development, it is reasonable to suppose that brain activity in the auditory cortex would differ substantially in deaf children deprived of sound for a long period of time and in children deprived of sound for a short period. This is, indeed, the case. Several groups have reported that the higher-order cortices can be cross-modally reorganized in deaf and blind subjects who have experienced long periods of sensory deprivation (Nishimura et al., 1999, 2000; Petitto et al., 2000; Finney et al., 2001; Lee et al., 2001; Neville and Bavelier, 2002; Roder et al., 2002). Some of these studies suggest that cross-modal reorganization in the auditory cortex limits the plastic adaptation of the cortex to afferent inputs from the auditory system, i.e., cochlear implants. On this view, the onset of cross-modal reorganization, perhaps at around age 7 years, signals the end of the sensitive period (e.g., Lee et al., 2001).

If there is different activity in the auditory cortices of children implanted within and beyond the sensitive period, then central auditory development following the onset of electrical stimulation should unfold in a different manner in early and late implanted, congenitally deaf children. To assess whether this is the case, we examined longitudinal changes in the P1 cortical evoked potential of congenitally deaf children who received unilateral or bilateral cochlear implants either before age 3.5 years or after age 7 years. The issue was whether, over time, the morphology and latency of cortical evoked responses from the two groups would exhibit similar patterns of development.

2. Materials and methods

2.1. Subjects

Subjects were 21 children with unilateral cochlear implants and two children with bilateral cochlear implants. All subjects were congenitally deafened, i.e., diagnosed with profound hearing loss by age 1 year. In 12 cases the etiology of the deafness was unknown, and in the other cases the etiology of deafness was due to cytomegalovirus (two cases), meningitis (two cases), maternal rubella (two cases), Waardenburg syndrome (two cases) and a cochlear malformation. The children were divided into two groups based on age of implantation. Twelve children who were implanted with a single multi-channel cochlear implant before age 3.5 years constituted the 'early-implanted' group and eight children who were implanted with a single multi-channel cochlear implant after age 7 years formed the 'late-implanted' group. For the early-implanted group, the mean age at implant activation was 1.77 years (range 1.01–3.33 years). For the late-implanted group, the mean age at implant activation was 11.7 years (range 7.95–17.53 years). The children were tested at the time of implant activation and then at approximately the following time periods: 1–3 weeks later, 1 month later, 3–4 months later, 6–9 months later and 12–24 months later. Not every child was able to attend every test session.

Two subjects had bilateral cochlear implants. One subject received her first implant at age 1.07 years and her second implant at age 2.07 years. The second subject received her first implant at age 2.08 years and was fitted with her second implant at age 10.10 years.

2.2. Stimuli

Cortical auditory evoked responses were recorded in response to a synthesized speech syllable /ba/. The duration of the speech sound was 90 ms. This stimulus was identical to the one used in Sharma et al. (1997, 2002a,b,c). The five formant CV stimulus was generated using the Klatt speech synthesizer. The starting frequencies of F1 and F2 were 234 and 616 Hz, respectively. The

center frequencies for the formants of the vowel /a/ were 769, 1232, 2862, 3600 and 4500 Hz for F1, F2, F3, F4 and F5, respectively. F3, F4 and F5 were steady-state formants. The amplitude of voicing was constant for 80 ms and fell linearly to 0 in the last 10 ms of the stimuli. The fundamental frequency began at 103 Hz, increased linearly to 125 Hz over 35 ms and then decreased to 80 Hz over 55 ms.

The stimulus was presented at an offset-to-onset interstimulus interval of 610 ms. The stimulus was delivered via a loudspeaker placed at an angle of 45° on the side of the implant. Subjects who wore bilateral implants were tested with each implant individually (while the second implant was turned off). Subjects implant processors were set at their usual settings and the older subjects typically informed us that they could hear the stimulus at a comfortable loudness level.

2.3. Evoked response recording procedures

Subjects were seated comfortably in a reclining chair placed in a sound booth. Younger children were seated on their parent's laps. Subjects watched a videotape movie or cartoon of their choice on a TV monitor placed in front of them in the sound booth. We have found this to be an effective way of engaging young subjects (see also Kraus et al., 1995). Evoked potentials were collected using a Compumedics® evoked potentials system. Silver/silver chloride cup electrodes were used for the recordings. The active electrode was placed at Cz. The reference electrode was placed on the non-implanted ear (or right ear in the case of bilateral implants) and ground on the forehead. Eye movements were monitored using a bipolar electrode montage (lateral outer canthus-superior outer canthus). The eye-blink monitoring electrode was placed on the non-implanted side (or the right side in the case of bilateral implants).

In a few children, the P1 response was obscured by the presence of a stimulus artifact in the first 100 ms of the recording. In these cases, the reference electrode was moved along the isopotential field of the artifact (typically around the forehead) to a point of null polarity, where the amplitude of the artifact was minimal and the P1 response was easily visualized (Finley, personal communication).

Averaging was automatically suspended by the recording computer when eye blinks were detected. The recording window included a 100 ms pre-stimulus and 600 ms poststimulus time. Responses were sampled at 1.0 kHz. Incoming evoked responses were analog filtered from 0.1 to 100 Hz. Approximately, two runs of 300 response sweeps were collected for each subject. The typical test session including electrode application and evoked response recording lasted for about 30 min.

2.4. Data analysis

Sweeps greater than ±100 μV were rejected offline, after that the remaining sweeps were averaged to compute an averaged waveform. Individual subjects had at least two averaged AEP waveforms of 300 sweeps each. If the waveforms were judged replicable based on visual inspection then the waveforms were averaged together to create a grand average waveform for individual subjects. P1 was defined as the first robust positivity in the waveform. Latency values were determined for P1 without regard to the age of implantation of subjects.

3. Results

3.1. Unilaterally implanted children

3.1.1. Waveform morphology

At the time of implant activation, the evoked responses of early-implanted children showed a large negativity that preceded the P1 component (see Fig. 1). The latency of this negativity was about 200 ms following the onset of stimulation. For late-implanted children, a large negativity also dominated the waveform at implant activation. The latency of this negativity was shorter (approximately 100 ms) than in early-implanted children.

The morphology of the waveforms from early- and late-implanted children differed markedly during the first year of electrical stimulation. In the early-implanted children the initial, large amplitude, negative component decreased in latency and became smaller over time. In late-implanted children the initial negativity changed only a little in latency and amplitude over the period 1 week to 12–19 months. For early-implanted children, the P1 component decreased in latency as experience with the implant increased. For late-implanted children, the P1 component changed little in latency after 1 month of stimulation.

Critically, for the late-implanted children the waveforms during most of the first year after implantation showed an atypical morphology, i.e., a nearly sinusoidal form. After about 12–18 months of implant use a more typical P1 response waveform was seen.

3.1.2. P1 latency

A partially repeated measure ANOVA was performed to examine the effect of duration of implant use and age of implantation on P1 latencies. Because P1 latencies were not available for all children at every designated time interval after implantation, a general linear model was used to interpolate data. Duration of implant use (activation, 1–3 weeks, 1
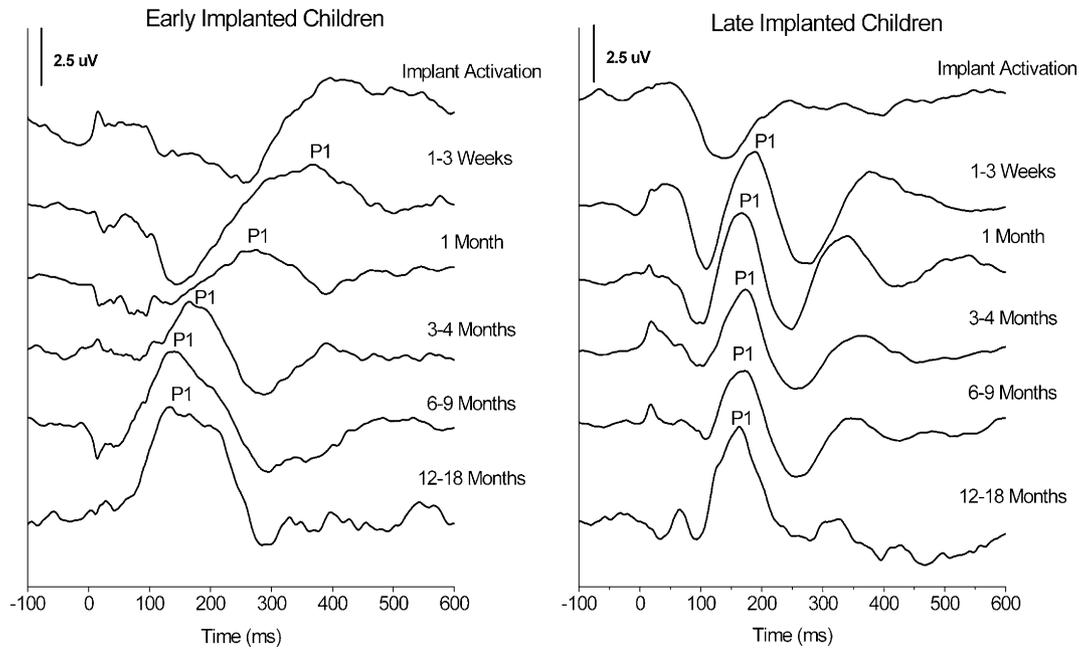
Fig. 1. Grand average waveforms for early and late-implanted children.

month, 3–4 months, 6–9 months, and 12–18 months) was treated as the within subjects variable and age of implantation (*early vs. late*) was treated as the between subjects variable. Duration of implant use can also be interpreted as '*time in sound*' (Ponton et al., 1996a,b).

Statistical analyses revealed a significant main effect of age of implantation ($F = 12.57$; $p = 0.002$) and a significant interaction between duration of implant use and age of implantation ($F = 15.24$; $p < 0.001$). Post hoc tests were used to assess the interaction between duration of implant use and age of implantation. A post hoc analysis of pairwise comparisons (Bonferroni correction for multiple comparisons) was performed in order to

compare changes in P1 latency with increased duration of implant use for the early- and late-implanted children. The mean values and the results of the post hoc comparisons are shown in Table 1. Individual data are shown in Fig. 2.

The two groups had significantly different P1 latencies at the time of implant activation. As shown in Fig. 3(a) the mean latency for late-implanted children was significantly ($p < 0.001$) shorter than for early-implanted children.

In order to further highlight the interaction between duration of implant use and age of implantation, we plot in Fig. 3(b) the change in mean P1 latency as a function of duration of implant use for the early and

Table 1

Mean P1 latencies are shown for early- and late-implanted children as a function of duration of implant use

Duration	Activation	1–3 Weeks	1 Month	3–4 Months	6–9 Months	12–18 Months
Early-implanted children						
Activation	378.18 (61.62)$					
1–3 Weeks	**	300.89 (41.03)				
1 Month	**	**	240.20 (37.21)			
3–4 Months	**	**	**	169.17 (10.87)		
6–9 Months	**	**	**	ns	133.20 (13.26)	
12–18 Months	**	**	**	ns	ns	137.50 (17.68)
Late-implanted children						
Activation	245.84 (52.08)$					
1–3 Weeks	ns	195.57 (38.38)				
1 Month	**	ns	160.28 (14.74)			
3–4 Months	*	ns	ns	175.98 (18.59)		
6–9 Months	*	ns	ns	ns	159.00 (14.57)	
12–18 Months	**	ns	ns	ns	ns	148.55 (21.52)

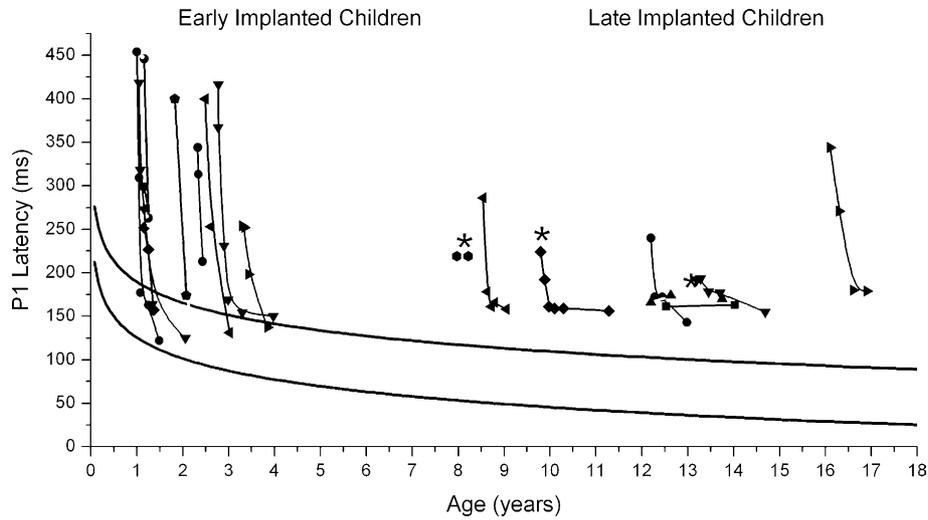SD are shown in parentheses. $,**$p < 0.001$; *$p < 0.01$; ns: not significant.

Fig. 2. Individual trajectories for P1 latency changes for the early- and late-implanted groups. In all subjects (except those indicated by asterisks) the initial data point was obtained at the time of implant activation. The solid lines represent the 95% confidence intervals for normal development of P1 latencies.
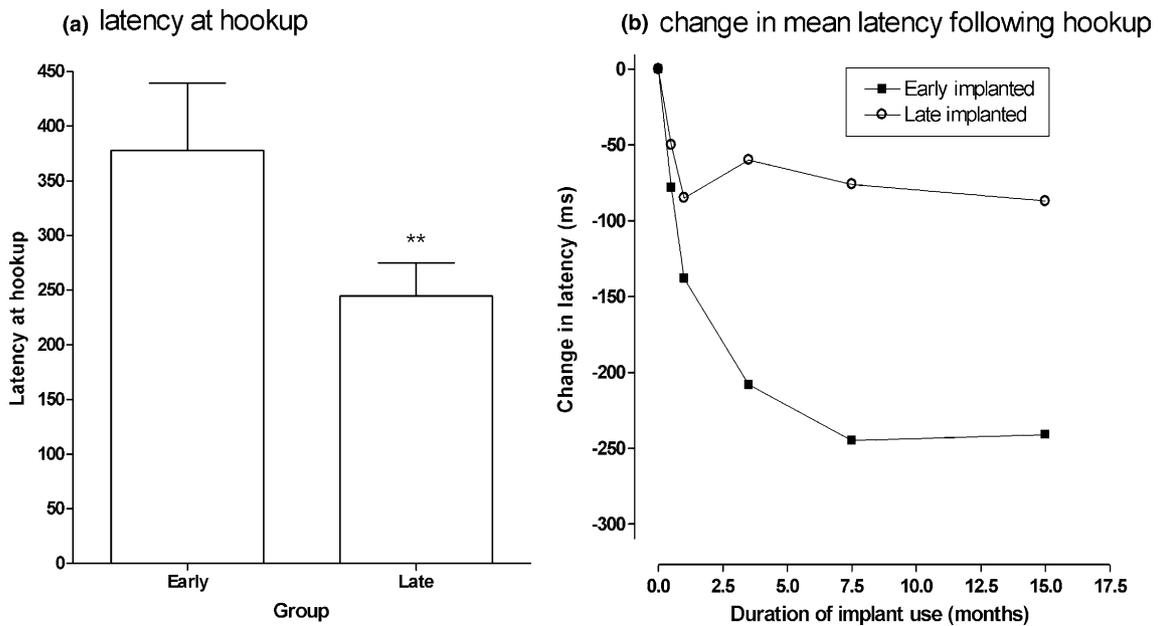

Fig. 3. (a) Mean P1 latency for the early- and late-implanted groups at the time of initial stimulation with the cochlear implant. (b) Changes in mean P1 latency following stimulation for the early- and late-implanted children are shown following normalization of starting latencies. The values on the x-axis are the mid points of the time intervals shown in Table 1.

late groups. In this figure latencies at hookup have been normalized. The values on the x-axis are the mid points of the time intervals shown in Table 1. Inspection of Fig. 3(b) indicates (i) that changes in latency following hookup are larger for the early-implanted children than for the late-implanted children and (ii) that changes in latency extend further in time for the early-implanted children than for the late-implanted children.

Both early- and late-implanted children showed a 35% decrease in P1 latency in the initial month after implantation. After that time, P1 latency for early-implanted children continued to decrease (mean decrease of 64% over the 12–18 month period following implantation). In contrast, for the late-implanted children latencies decreased significantly (35%) only over the first month of stimulation and then reached a plateau (mean decrease of 39% in 12–18 month period following implantation).

3.2. Bilaterally implanted children

Longitudinal P1 latency data from two sequentially bilaterally implanted children are shown in Figs. 4 and 5. Subject 1 (Fig. 4) received her first implant at age 1.07 years and her second implant at age 2.07 years. As expected, after several months experience with the first implant, P1 latencies were within normal limits. The P1 latency elicited by the second implant was within normal limits after 1 month of experience with bilateral implants. The data from both ears fit the profile of a patient implanted within the sensitive period.

Subject 2 (Fig. 5) received her first implant at age 2.08 years and was fitted with her second implant at

Fig. 4. Trajectories for P1 latency changes following sequential bilateral implantation for Subject 1. The solid lines represent the 95% confidence intervals for normal development of P1 latencies.

Fig. 5. Trajectories for P1 latency changes following sequential bilateral implantation for Subject 2. The solid lines represent the 95% confidence intervals for normal development of P1 latencies.

age 10.10 years. As expected, when tested with the first implant after 7 years of stimulation, the P1 latency was within normal limits. In contrast, the P1 latencies recorded in response to stimulation via the second implant were delayed even after 9 months of bilateral implant use.

4. Discussion

We have examined the longitudinal development of the P1 cortical response in groups of early- and late-implanted children. The age cut-offs for the two groups (<3.5 years for early-implanted and >7 years for late-implanted) were based on the sensitive period for central auditory development described by Sharma et al. (2002c). Our results show a markedly different pattern of P1 development for early and late implanted children.

4.1. Early-implanted children

For early-implanted children, at implant activation the waveform was dominated by a large negativity preceding the P1 response. We have seen this negativity consistently in congenitally deaf children at the time of implantation and in profoundly hearing-impaired children at the time of initial fitting with a hearing aid (Sharma et al., 2004). This early negativity is strikingly similar to the 'long-latency negative potential' reported in studies on preterm infants before 25 weeks postconception (Salamy et al., 1984; Weitzman et al., 1967). The similarity suggests that CAEP morphology and latency at the time of implantation can be interpreted as a sign of a naive (i.e., unstimulated) auditory system. Alternately, the early negativity may reflect involvement of the non-primary auditory areas in the generation of the cortical auditory evoked potential in the absence of sensory input to the primary auditory pathways (Kraus and McGee, 1995; Møller and Rollins, 2002).

For early-implanted children, there was a large and rapid decrease in P1 latency (approximately 100 ms) within a week of cochlear implant usage. The rapid change in the state of the auditory pathway is consistent with rapid changes in the visual pathways following the onset of patterned visual stimulation after the removal of congenital cataracts. Maurer et al. (1999) report an improvement in acuity with as little as an hour of patterned visual input.

One week after implant use P1 latencies were similar to those of normal-hearing newborns. The early negativity preceding P1 seen in children with little auditory experience diminished in amplitude and latency with more auditory experience. Within 6–8 months of age P1 latencies reached normal limits. This outcome is consistent with our previous findings (Sharma et al., 2002a).
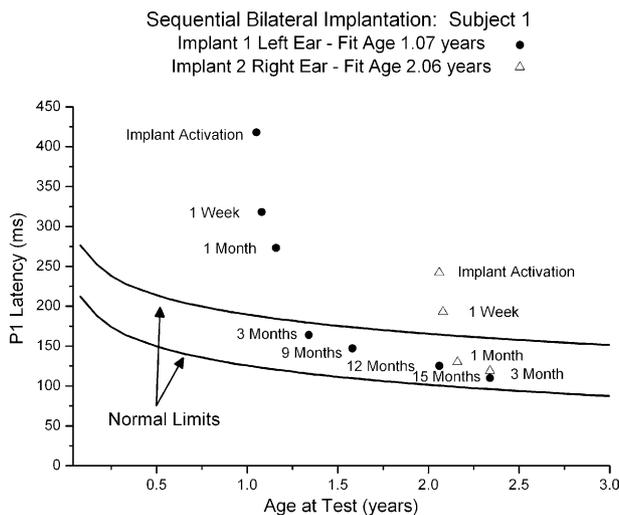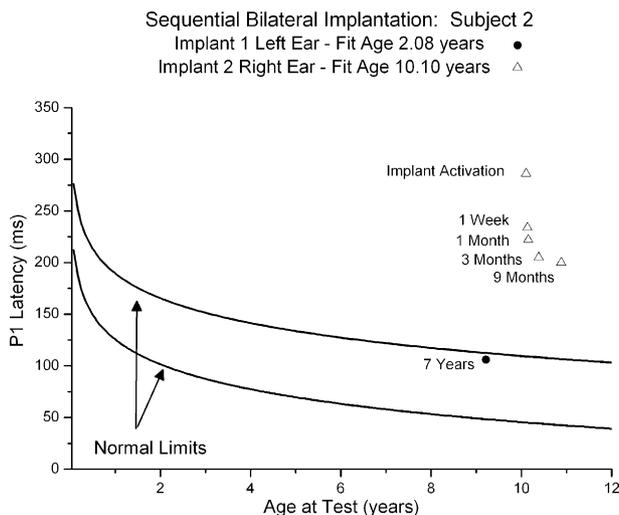
The neurophysiologic mechanisms underpinning these changes in P1 latency are not clear. However, Kral et al. (2000) have shown that congenitally deaf cats (i) show a restricted (atypical) pattern of activation within the layers of the primary auditory cortex compared to normal-hearing cats and (ii) show signs of desynchronization of activity among different cortical layers. As a consequence, there are changes in morphology of local field potentials recorded at the cortical surface. If similar processes are at work in young deaf children, then we can hypothesize that a change in interaction between different cortical layers, driven by the onset of electrical stimulation, results in a rearrangement in the generators of the P1 response (for cats, see Klinke et al., 1999). Such a process, which would be maximized during the period of synaptic overshoot (Kral et al., in press), is likely to be the major factor in the rapid changes in waveform morphology and the latency that we have found.

4.2. Late-implanted children

Late-implanted children show a different pattern of central auditory development than that shown by early implanted children. The early negativity linked with auditory deprivation dominates the waveform at the time of implant activation. In late-implanted children the initial negativity occurs at a shorter latency than the initial negativity in early-implanted children. It is also the case that the P1 latency at implant activation is shorter in late-implanted children than in early-implanted children. Both outcomes suggest that there is some degree of intrinsic development of the central auditory pathways in the absence of stimulation. This outcome is consistent with the findings of Kral et al. (in press) who showed that middle and long-latency responses appeared early in development in naive congenitally deaf cats even in absence of any auditory inputs, although the further development differed significantly from development in hearing controls. Correspondingly, in late-implanted children, the polyphaisc morphology of the cortical evoked waveform response is atypical and remains atypical for several months following the onset of stimulation. Gradually between the 12th and 18th months after implantation, the morphology of the waveform becomes more typical for late-implanted children.

4.3. Two-processes in development

The relative change in P1 latency between hookup and one month was the same (35%) for early and late-implanted children (see Fig. 3(b)). Thus an early, input-dependent maturation process in P1 latency is comparable between early- and late-implanted children. However, after approximately 4 weeks of stimulation, the maturation process becomes arrested in late-implanted children, but continues in early-implanted children. The initial, rapid change in latency for both groups could be related to synaptic processes like long-term potentiation. The continuing change in latency for the early-implanted children could be related to structural rearrangement of synaptic contacts (synaptic formation and elimination). Only the latter process demonstrates a sensitive period.

Given the difference in the morphology of the CAEP waveform between the early- and late-implanted children, it is possible that the peak that we have labeled as P1 does not have the same generator for the two groups. Future studies should examine this possibility using multi-channel recordings. In the present study it is useful to label the first, large, positive component as P1 for the two groups as this allows us to quantitatively compare the development of cortical activity across the groups following the onset of electrical stimulation.

Duration of implant use is obviously critical for development of the central auditory pathways following implantation (Ponton et al., 1996a,b, 2001). The present results emphasize the interaction of duration of implant use with age of implantation and speak to the importance of an early sensitive period. Together these factors shape cortical development (or responsiveness) after implantation.

Our results suggest that both the latency and morphology of the P1 response serve as markers for the developmental status of central auditory pathways. We currently use the P1 response as a clinical tool for assessment of central auditory development in hearing-impaired and cochlear-implanted children.

4.4. Bilateral implantation

The present study describes, for the first time, cortical development in children with bilateral cochlear implants. Because only two children have been investigated these results have to be treated as case reports.

One child received both her first and second implants within the sensitive period. The second child received her fist implant within the sensitive period and received her second implant after the end of the sensitive period. Our interest in these cases was in the effects on central auditory development of stimulation contralateral and ipsilateral to the early-implanted ear.

Figs. 4 and 5 show longitudinal P1 latency data from the two children. The subject shown in Fig. 4 received her first implant at age 1.07 years and her second implant at age 2.07 years. As expected, after several months experience with the first implant, P1 latencies were within normal limits. Based on animal studies (Kral et al., 2002) we assume that the P1 response reflected activity mainly from the cortex contralateral to the implanted ear. At the time of

activation of the second implant, the P1 latency was shorter than the P1 latency recorded from the first implant at activation. This suggests either a beneficial effect of stimulation ipsilateral to the first implanted ear, age-related intrinsic development, or both. However, the response was delayed relative to normal suggesting a 'weak' activation of the ipsilateral pathway. This speculation is consistent with findings from implanted kittens (Kral et al., 2002). The P1 latency elicited by the second implant was within normal limits within a very short period (1 month) of implant use suggesting rapid development of the central auditory pathways when both implants are fitted within the sensitive period.

The subject in Fig. 5 received her first implant at age 2.08 years. As expected, after 7 years of stimulation the P1 latency was within normal limits. The child was fitted with her second implant at age 10.10 years. At hookup the P1 latency was similar to that of children who received their first implant at age 10. This demonstrates that long-term stimulation from the first implant had only a limited influence on the development of the central auditory system ipsilateral to the first implant. This outcome might arise if the early (primary) auditory cortical areas ipsilateral to the first implant are stimulated by both ears, but the higher-order areas generating the P1 waves evoked by the first implant are connected only to the cortex contralateral to the first implant. Alternatively, the entire pathways activated by the two ears might remain (or become) functionally segregated in the congenitally deaf. More research with multi-electrode recordings is necessary to account for our outcome.

The trajectory of P1 latency change for stimulation through the second implant was similar to the trajectories shown in Fig. 2 for late-implanted children. This, once again, suggests limited benefit to central auditory development from stimulation ipsilateral to the implanted ear. We note also that the morphology of the waveforms elicited via the two implants differed markedly. The waveform elicited in response to stimulation from the second implant displayed a polyphasic form similar to that seen in late-implanted, congenitally deaf children. Taken together, these outcomes suggest that long-term stimulation of auditory pathways ipsilateral to an implant is not sufficient to preserve the plasticity of those pathways. If this is the case, then the stimulation from a second late implant will be to a cortex which does not have normal connections within cortical layers and which does not have normal connections to higher-order auditory and language cortex. The benefit of such an implant may be very limited.

4.5. Cortical mechanisms underlying the sensitive period

In the introduction we speculated that auditory development would proceed differently in deaf children deprived of sound for a short period – less than 3.5 years – and in deaf children deprived of sound for a long period – greater than 7 years – because of a brief sensitive period for normal development of central auditory pathways. In the present study, using the morphology and latency of the P1 cortical evoked potential as measures of development, we find that development does indeed proceed in a different manner in the two samples of deaf children. Our finding of different developmental histories for early- and late-implanted children is bolstered by results from another measure – the N1 component of the cortical evoked response. Preliminary results suggest that children implanted within the sensitive period show an age-appropriate N1 response while those implanted after age 7 years do not (Gilley et al., 2004). These data are in contrast to other studies which report the absence of an N1 in cochlear implanted children (Ponton and Eggermont, 2001; Singh et al., 2004).

Given the differences in development in early- and late-implanted children we should ask, "What is different in terms of cortical activity during and after the end of the sensitive period?" Congenitally deaf cats are a model system for cortical activity after the end of the sensitive period. In kittens, the sensitive period for development of central auditory pathways lasts up to 5 months of age (Kral et al., 2002). When electrical stimulation is started after 4 months of deafness there is a delay in the activation of supragranular layers and a near absence of activity at longer latencies and in infragranular layers (layers V and VI) (Kral et al., in press). The additional, near-absence of outward currents in layers IV and III of congenitally deaf cats suggests incomplete development of inhibitory synapses and an alteration of information flow from layer IV to supragranular layers. This abnormal pattern of activity within the auditory cortex is likely to be the basis for differences in evoked potential morphology and latency we find in children implanted during the sensitive period and after the end of the sensitive period. Because the higher-order auditory cortex projects back to A1 (primary auditory cortex) mainly to the infragranular layers, the absence of activity in infragranular layers suggests a decoupling of primary cortex from higher order auditory cortex. Such a decoupling would allow other sensory input to predominate in the higher-order auditory cortex in children deprived of sound for a long period. This supposition is consistent with the functional imaging data from deaf children reported by Lee et al. (2001). The hypothesis of a decoupling of primary cortex from higher order auditory and language cortex in children deprived of sound for a long period provides an account for the language learning difficulties of children who receive an implant after the end of the sensitive period.

Acknowledgements

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