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Cortical development, plasticity and re-organization in children with cochlear implants

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Abstract

A basic tenet of developmental neurobiology is that certain areas of the cortex will reorganize, if appropriate stimulation is withheld for long periods. Stimulation must be delivered to a sensory system within a narrow window of time (a sensitive period) if that system is to develop normally. In this article, we will describe age cut-offs for a sensitive period for central auditory development in children who receive cochlear implants. We will review de-coupling and reorganization of cortical areas, which are presumed to underlie the end of the sensitive period in congenitally deaf humans and cats. Finally, we present two clinical cases which demonstrate the use of the P1 cortical auditory evoked potential as a biomarker for central auditory system development and re-organization in congenitally deaf children fitted with cochlear implants.

Learning outcomes—Readers of this article should be able to (i) describe the importance of the sensitive period as it relates to development of central auditory pathways in children with cochlear implants, (ii) discuss the hypothesis of decoupling of primary from higher order auditory cortex as it relates to the end of the sensitive period, (iii) discuss cross-modal reorganization which may occur after long periods of auditory deprivation, and (iv) understand the use of the P1 response as a biomarker for development of central auditory pathways.

Keywords

Cochlear Implants; Children; P1; CAEP; Sensitive Period

1. Introduction

An important question in the field of pediatric aural rehabilitation is, “When is the optimal time to provide a young congenitally deaf child with a cochlear implant (CI)?” Neuroscientific research has given us some insight into this question, with new information about sensitive periods, factors that lead to deterioration of the central auditory pathways, characteristics of plasticity in a maturing brain, and cortical re-organization that can occur when stimulation patterns differ from the norm.

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It is well known that there are critical or sensitive periods for neurobiological development in the brain (for a review, see Bischof, 2007). In the auditory system, a sensitive period for the development of the central auditory system is a time during which the central auditory pathways are maximally plastic and primed for stimulation-driven development. Therefore, it is reasonable to presume that cochlear implantation that occurs within this sensitive period would achieve optimal results.

One way to objectively measure the developmental status and limits of plasticity of the auditory cortical pathways is to examine the latency of cortical auditory evoked potentials. In particular, the latency of the first positive peak (P1) of the CAEP in children is considered a biomarker for maturation of the auditory cortical areas (Eggermont & Ponton, 2003; Sharma & Dorman, 2006; Sharma, Gilley, Dorman, & Baldwin, 2007). The P1 is a robust positivity occurring at around 100–300 milliseconds in children. Latency of the P1 reflects the sum of synaptic delays throughout the peripheral and central auditory pathways (Eggermont, Ponton, Don, Waring, & Kwong, 1997). The P1 peak latency varies as a function of age, and is therefore considered an index of cortical auditory maturation (Ceponiene, Cheour, & Naatanen, 1998; Cunningham, Nicol, Zecker, & Kraus, 2000; Gilley, Sharma, Dorman, & Martin, 2005; Ponton, Eggermont, Khosla, Kwong, & Don, 2002; Sharma, Dorman, & Spahr, 2002a; Sharma, Kraus, McGee, & Nicol, 1997). Evidence from intracranial recordings in humans, as well from animal models, suggests that the neural generators of the P1 CAEP originate from the thalamo-cortical projections to the auditory cortex and may represent the first recurrent activity in the auditory cortex (Kral & Eggermont, 2007; Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994; Ponton & Eggermont, 2001). Given that auditory input first reaches the auditory cortex as early as 20–30 ms after stimulation (as reflected in the auditory middle latency response (MLR) (Kraus & McGee, 1993; McGee, Kraus, Comperatore, & Nicol, 1991), it would be reasonable to assume that early components of the CAEP such as the P1 (and N1), which have longer latencies in childhood, reflect second order processing in the auditory cortex, including input from feedback and recurrent loops between primary auditory and association areas (Sharma et al., 2007).

Sharma and colleagues have established a normal range for the latency of the P1 waveform peak at different ages (Sharma et al., 2002a). A newborn may have a P1 peak latency of around 300 ms. Rapid development during the first 2–3 years leads to a rapid decrease in P1 latency: 3 year olds have a P1 latency of about 125 ms. Adults have a P1 latency of around 60 ms.

The P1 response has been measured in deaf children who received cochlear implants at different ages to examine the limits of plasticity in the central auditory system (Ponton, Don, Eggermont, Waring, & Masuda, 1996; Ponton & Eggermont, 2001; Sharma, Dorman, & Kral, 2005; Sharma, et al., 2002a; Sharma, Dorman, & Spahr, 2002b; Sharma, et al., 2007). Sharma and colleagues (2006) examined P1 latency in 245 congenitally deaf children fit with a CI, and reported that children who received CI stimulation early in childhood (< 3.5 years) had normal P1 latencies, while children who received CI stimulation late in childhood (> 7 years) had abnormal cortical response latencies. A group of children receiving CIs between 3.5 and 7 years revealed highly variable response latencies. In general, for the majority of late-implanted children, response latencies did not reach normal limits even after several years of experience with the implant, consistent with Sharma, Dorman, and Kral (2005) and Sharma et al. (2007). Waveform morphologies are another measure of development following the onset of stimulation. In the early implanted children of Sharma and Dorman (2006), waveform morphology was normal and characterized by a broad positivity within a week following the onset of stimulation. For the late implanted children, waveforms were commonly abnormal and characterized by a polyphasic waveform or a generally low amplitude waveform. Figures 1 – 3 (from our clinical case section) provide examples of these waveform patterns. Overall, our P1 data suggest a sensitive period for central auditory development of about 3.5 years.

There is some variability in the data from ages 3.5 to 7 years. However, in all likelihood, the sensitive period ends at age 7 years. This finding of a sensitive period for central auditory development in humans is consistent with other studies in animals (Kral, Hartmann, Tillein, Heid, & Klinke, 2000, 2001; Ryugo, Pongstaporn, Huchton, & Niparko, 1997) and in humans (Eggermont & Ponton, 2003; Lee, et al., 2001; Schorr, Fox, van Wassenhove, & Knudsen, 2005). Consistent with our age cut-offs for the sensitive period inferred from P1 latencies, studies have shown that children implanted under age 3–4 years show significantly better speech and language skills than children implanted after 6–7 years (Geers, 2006; Kirk, et al., 2002).

1.1 Cortical decoupling

Studies in congenitally deaf cats have established a possible mechanism for the end of the sensitive period. When electrical stimulation is started after 4–5 months of deafness, i.e., after the end of the sensitive period for central auditory development in cats, there is a delay in the activation of supragranular layers of the cortex and a near absence of activity at longer latencies and in infragranular layers (layers V and VI) (Kral, Tillein, Heid, Hartmann, & Klinke, 2005). The 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. The higher order auditory cortex projects back to A1 (primary auditory cortex) mainly to the infragranular layers and the infragranular layers (V and VI) send long range feedback projections to the subcortical auditory areas. The absence of activity in infragranular layers can be interpreted to suggest a functional decoupling of primary cortex from higher order auditory cortex, also affecting feedback projections to subcortical auditory structures (Kral, et al., 2000; Kral, Hartmann, Tillein, Heid, & Klinke, 2002; Kral, et al., 2005). That is, with a lack of typical auditory experience, infragranular activity is severely compromised, projections from secondary auditory areas back to the primary auditory areas do not develop properly, and these important feedback loops are weakened. The secondary auditory areas are decoupled from the primary auditory areas, and are no longer able to provide important cognitive, “top-down” modulation (Kral & Eggermont, 2007). The decoupling of primary and secondary auditory areas may actually make the secondary areas more available to other modalities in the process of re-organization. These mechanisms are cited by Kral (2007) as the reasons auditory processing becomes difficult after the sensitive period; specifically, modulation of the primary auditory areas is changed (affecting plasticity), and cortical areas important for auditory and linguistic processing area are re-purposed by other systems, making it challenging for any new incoming auditory stimuli to be analyzed efficiently.

1.2. Human cortical reorganization

The decoupling hypothesis in congenitally deaf cats (described above) posits that the secondary cortical areas are re-organized by other modalities after the end of the sensitive period. It would be useful to determine if a similar mechanism underlies the end of the sensitive period in humans.

Gilley et al. (2008) used high density EEG measures and analyzed the brain source localization of the CAEP in response to a speech sound to document the areas of activation in the cortices of normal hearing children and age-matched children who received cochlear implants before and after the sensitive period age cut-offs described by Sharma et al. (2002a). Normal hearing children showed, as expected, bilateral activation of the auditory cortical areas (superior temporal sulcus and inferior temporal gyrus). Children who received cochlear implants at an early age (<3.5 years of age at fit) showed activation of the auditory cortical areas contralateral to their cochlear implant which resembled that of normal hearing subjects, for the most part (additionally a minor source of activity was localized to the anterior parietotemporal cortex).

However, late-implanted children (>7 years fit age) showed activation outside the auditory cortical areas (visual, insula and parietotemporal areas). If we assume that generators of early components of the CAEP include input from intracortical and intercortical recurrent activity between primary auditory and association areas, then abnormal or absence of auditory cortical activity in the late implanted children in the Gilley et al. (2008) study suggests absent or weak connections between primary and association areas, and subsequently, weak feedback activity to thalamic areas. These results are consistent with Kral's decoupling hypothesis (Kral et al., 2005) which suggests that a functional disconnection between the primary and higher order cortex underlies the end of the sensitive period in congenitally deaf cats, and presumably, in congenitally deaf, late-implanted children.

Partial or complete decoupling of the primary and secondary cortices leaves the secondary cortex open to re-organization by other modalities (i.e., cross-modal re-organization). The seminal work of Neville and colleagues (Bavelier & Neville, 2002; Bavelier, et al., 2000; Eggermont & Ponton, 2003; Klinke, Hartmann, Heid, Tillein, & Kral, 2001; Kral, et al., 2000, 2002; Kral, et al., 2005; Lebib, Papo, de Bode, & Baudonniere, 2003; LeVay, Wiesel, & Hubel, 1980; Neville & Bavelier, 2002; Ponton & Eggermont, 2001; Roder, Rosler, & Neville, 1999, 2000, 2001; Roder, Stock, Bien, Neville, & Rosler, 2002) as well as recent neuro-imaging studies (Fine, Finney, Boynton, & Dobkins, 2005; Finney, Clementz, Hickok, & Dobkins, 2003; Finney, Fine, & Dobkins, 2001; Sharma et al., 2007) provide clear evidence of visual and somatosensory activation of higher-order auditory cortex suggesting cross-modal re-organization of higher order auditory cortex. For example, Fine et al. (2005) used functional magnetic resonance imaging (fMRI) to assess activation patterns in normal hearing users with fluency in American Sign Language (ASL), normal hearing nonsigners, and deaf users of ASL in response to visual stimuli. Visual stimuli activated areas within the auditory cortices of deaf ASL users that were not activated in normally hearing subjects (signing or nonsigning). No difference was found between deaf and hearing participants in activation or attention modulation in the visual cortex. Since activation of the auditory cortex in response to visual stimuli was limited to the deaf participants, the researchers suggest that the effects they measured were driven by auditory deprivation rather than exposure to sign language. Attention to visual stimuli increased the activation of the auditory cortex seen in deaf participants, which suggested input from higher level association areas, consistent with the decoupling hypothesis of Kral and colleagues (2005).

In another study, (Sharma et al., 2007) magnetoencephalographic (MEG) brain activity was recorded in a normal hearing and deaf adult during vibrotactile stimulation to the hand. Brain source analysis of the averaged evoked potentials revealed bilateral activation of somatosensory cortex in the normal hearing adult. However, in response to vibrotactile stimulation, the deaf adult showed bilateral activation in the somatosensory cortex, as well as in the posterior regions of the superior temporal sulci bilaterally. That is, in the deaf adult, somatosensory stimuli activated areas of the auditory multimodal/association cortex. Results of these studies suggest at least some cross-modal plasticity and reorganization between visual, somatosensory and auditory areas is likely after prolonged periods of auditory deprivation.

1.3 Clinical evidence of cortical development and re-organization using the P1 CAEP biomarker

Our longitudinal studies of nearly 1000 children with normal hearing, hearing aids and cochlear implants have revealed patterns in the CAEP waveform which are reasonably easy to identify and are predictive of abnormalities in the central auditory maturation. Some examples of these are shown in Fig. 1.

In Fig. 1 the waveform of the CAEP obtained from young, normal- hearing child shows a robust initial positivity depicting the P1 component (top trace).

CAEP waveforms from young children who have a severe-to-profound hearing loss are dominated by an initial large negativity (second from the top trace). We consider this 'deprivation negativity' to be the hallmark of an unstimulated, or little stimulated, yet plastic central auditory pathway.

For children who have a less severe degree of hearing impairment, and in whom the auditory pathways have been stimulated to some extent, but not optimally, the waveform is dominated by a P1 response, with a delayed latency relative to normal (third trace from top).

Polyphasic waveforms (bottom trace) are often obtained in older deaf children and in some non-implanted ears of older, unilaterally implanted children. We believe that the polyphasic morphology is characteristic of a central auditory system that has developed abnormally and/or re-organized due to deprivation.

Using these distinctive patterns of the P1 response as markers of central auditory system development we describe two cases of children implanted before, and after the sensitive period for central auditory development.

2. Clinical cases

2.1 Case 1

The patient is a ten year old child who was diagnosed with congenital profound hearing loss after failing a newborn hearing screening. He was fitted at age 4 months with hearing aids which he continued to use until cochlear implantation at age 1.4 years, that is, well within the sensitive period for central auditory development.

Fig. 2 shows the cortical auditory evoked potential waveform recorded from this child. Recording procedures and analysis methods were similar to those described in our previous studies (Sharma et al., 2002a,2002b;2005). The initial robust positivity reflects the P1 component, which showed an age-appropriate morphology. Latency of the P1 response was within normal limits when compared to the 95% confidence intervals for normal development of P1 latency (from Sharma et al., 2002a).

Given the early age of implantation and normal development of the central auditory pathways following implantation, we would expect good behavioral outcomes for this child. His scores of 92% on the Lexical Neighborhood Test (LNT- Lexically Hard) of speech perception in quiet and of 7.7 dB SNR-50 (a score comparable to age-matched normal hearing listeners) on the BKB-SIN speech in noise test are considered excellent for a cochlear implanted child of his age. In this case, a child implanted within the sensitive period for central auditory development showed normal CAEP waveform morphology and P1 latency suggesting age-appropriate development of auditory cortical areas. Excellent performance on speech perception tests in quiet and in noise further cross-validated the P1 results.

2.2 Case 2

The patient was a female child with an unremarkable birth in a foreign country who was diagnosed with severe-to-profound hearing loss after a bout of meningitis at two months of age. Her primary form of communication was sign language in early childhood. She was fitted with hearing aids after moving to the United States at age 4 years, but was reported as wearing her hearing aids inconsistently. She received a cochlear implant at age 7.4 years, that is, after the end of the sensitive period for central auditory development.

CAEP waveforms were recorded six months post implantation. Fig. 3 shows a polyphasic waveform suggesting an abnormally developing or re-organized auditory cortex which

typically occurs after the end of the sensitive period (Sharma et al., 2005). Given P1 evidence of a reorganized cortex, we would hypothesize that this child was not likely to be a good performer with her implant. As expected, speech perception performance with her implant was minimal. She showed no evidence of pattern perception, placing her in Category 1 on the CID scales for early communication skills for hearing impaired children. She also revealed a low score (52%) on the IT-MAIS, a parent report measure usually used for infants and toddlers.

In this case of a child implanted at a late age in childhood, polyphasic CAEP waveforms (indicating a re-organized auditory cortex) were consistent with the patient's poor behavioral outcomes.

3. Summary

In this brief review, we have described CAEP studies of congenitally deaf children fitted with cochlear implants which describe the existence of, time limits for, and mechanisms which, underlie a sensitive period for the development of central auditory pathways. Based on our findings and as illustrated in the two case studies, the optimal time to implant a young congenitally deaf child with a unilateral cochlear implant is within the first 3.5 years of life when the central pathways show maximal plasticity. After the sensitive period ends (at around age 7 years), there is a high likelihood of de-coupling of the primary auditory cortical areas from surrounding higher order cortex and cross-modal re-organization of secondary cortical areas.

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Appendix A. Continuing education (*correct answer)

1. The P1 central auditory evoked potential peak has a latency of approximately _____ milliseconds in children.
 - a. 20–50
 - b. 50–100
 - c. 100–300*
 - d. 300–400
2. An absence of activity in the infragranular layers of the brain after a period of auditory deprivation suggests:
 - a. a decoupling of primary cortex from higher order auditory cortex and compromised feedback projections to subcortical auditory structures*
 - b. a functional loss of “bottom-up” modulation
 - c. a lack of cross-modal re-organization within the auditory cortex
 - d. plasticity in the primary and higher order auditory cortices has been maintained

3. What age appears to be the upper limit for the optimal time frame for receiving a unilateral cochlear implant based upon studies of the sensitive period in this population?
 - a. 2 years of age
 - b. 5 years of age
 - c. 3.5 years of age*
 - d. 10 years of age
4. In a study by Fine et al. that used fMRI to evaluate areas of the brain that are active in deaf users of ASL, normal-hearing users of ASL, and normal hearing non-users of ASL:
 - a. visual stimuli activated areas within the auditory cortex that were not activated in normally hearing ASL users or normally hearing non-users*
 - b. visual stimuli activated the same areas of the cortex as normally hearing ASL users
 - c. the auditory cortex was not activated in any of the three groups
 - d. the visual cortex was more active in deaf ASL users than the other two groups
5. What type of P1 CAEP waveform morphology may be observed in a patient with a reorganized cortex?
 - a. compound
 - b. polycortical
 - c. stratosinusoid
 - d. polyphasic*

Fig. 1. Examples of P1 waveforms for a normally developing central auditory pathway (top), an unstimulated central auditory system, (second from top), a partially stimulated central auditory system loss (third from top), a re-organized auditory cortex (bottom).

Fig. 2.
P1 CAEP response for an early implanted child which shows age-appropriate morphology and latency.

Fig. 3.
CAEP response recorded from a late-implanted child which shows evidence of polyphasic morphology.