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### Deprivation-induced cortical reorganization in children with cochlear implants

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## Key Words

Cochlear implants  
Plasticity  
Reorganization  
Cross-modal plasticity  
Cortical auditory evoked potentials  
(CAEP)  
Magnetoencephalography (MEG)  
Central auditory development, P1

## Abbreviations

CAEP: Cortical auditory evoked  
potential  
EEG: Electroencephalography  
MEG: Magnetoencephalography  
sLORETA: Standardized low  
resolution electromagnetic brain  
tomography  
MRI: Magnetic resonance imaging  
fMRI: functional magnetic  
resonance imaging

# Deprivation-induced cortical reorganization in children with cochlear implants

## Abstract

A basic finding in developmental neurophysiology is that some areas of the cortex reorganize following a period of stimulus deprivation. In this review, we discuss mainly electroencephalography (EEG) studies of normal and deprivation-induced abnormal development of the central auditory pathways in children and in animal models. We describe age cut-off for sensitive periods for central auditory development in congenitally deaf children who are fitted with a cochlear implant. We speculate on mechanisms of decoupling and reorganization which may underlie the end of the sensitive period. Finally, we describe new magnetoencephalography (MEG) evidence of somatosensory cross-modal plasticity following long-term auditory deprivation.

## Sumario

Un hallazgo básico en neurofisiología del desarrollo es que algunas áreas de la corteza se reorganizan después de un período de privación de estímulos. En esta revisión, discutimos predominantemente sobre estudios electroencefalográficos (EEG) de desarrollo normal y de desarrollo anormal inducido por privación de las vías auditivas centrales en niños y en modelos animales. Describimos cortes de edad para períodos sensibles de desarrollo auditivo central en niños congénitamente sordos, a quienes se les ha colocado un implante coclear. Especulamos sobre los mecanismos de desacople y reorganización que pueden imperar al final del período sensible. Finalmente, describimos nuevas evidencias magnetoencefalográficas (MEG) de la plasticidad de modalidad cruzada luego de una privación auditiva de largo plazo.

The development of sensory pathways in the cortex is determined by both intrinsic and stimulus-driven factors. Because both factors influence development the absence of sensory input, as in deafness, impedes the normal growth and connectivity needed to form a functional sensory system. Because normal function of the central pathways is a precondition for normal development of speech and language skills, children with hearing loss are at risk for abnormal development of these skills.

Cochlear implants (CIs) bypass peripheral cochlear damage, directly stimulate cell bodies in the spiral ganglion and make it possible, in principle, to avoid the deleterious effects of stimulus deprivation. From this point of view, children and adults who receive CIs provide a platform from which we can examine the

time course of, and constraints on, plasticity in the central auditory system. As we will document in this chapter, studies of children fitted with CIs at different ages provide strong evidence for a sensitive period in early childhood, the end of which is marked by cortical reorganization. Stimulation must be delivered to the auditory system within this sensitive period if normal cortical development is to take place.

In this review we will focus, principally, on cortical evoked potential (CAEP) measures of central auditory system function, and (1) summarize studies that have examined normal development of central auditory pathways, (2) summarize studies that have examined the development of central auditory pathways following auditory deprivation in humans and in animal models,

(3) summarize studies that have examined cross-modal plasticity or reorganization following auditory deprivation, and (4) speculate on the roles of decoupling and competition for cortical resources as they relate to deprivation induced cortical reorganization.

### Normal development of central auditory pathways

Intrinsic development of central pathways occurs as a function of biological programs that operate independently of stimulus input. For example, axonal growth cones in the central nervous system appear to have predetermined destinations for synaptic termination (Sanes & Yamagata, 1999; Bolz & Castellani, 1997; Castellani & Bolz, 1997) and synaptic terminals at the Calyx of Held in the brainstem have been shown to form prior to the onset of hearing in animal models (Lee et al, 2003; Ryugo et al, 1997).

The refinement of auditory pathways in the cortex is also driven, at least in part, by stimulation (including its frequency composition) from the auditory periphery, and by input from the basal forebrain that signals the behavioral importance of stimulation (Kral et al, 2000; Kral et al, 2001; Klinke et al, 2001; Kilgard et al, 2001; Kilgard & Merzenich, 1998). For example, tonotopic organization of the auditory cortex can be shaped by overexposure to a narrow range of stimuli during early postnatal development, demonstrating functional development specific to the acoustic environment (Zhang et al, 2001). Kilgard & Merzenich (1998) paired auditory stimulation with electric stimulation of the nucleus basalis in rats, and compared the resulting auditory cortical maps to maps created without nucleus basalis stimulation. The cortical maps were significantly altered (enlarged) when signals were paired with nucleus basalis stimulation and the alterations were specific to the nature of the stimulation being delivered, e.g. maps were different for modulated tones versus unmodulated tones, and for single tones versus multiple tones. Critically, the repeated presentation of behaviorally irrelevant signals did not produce changes in the cortical maps.

Changes in cortical auditory pathways, or maps, in response to stimulation can occur over both short and long time spans. The mechanisms underlying the two types of changes are likely mediated by different factors, e.g. the balance of excitatory and inhibitory stimulation over the short term, and restructuring of dendrites and axons over the long term (e.g. Darian-Smith & Gilbert, 1994).

Long-term restructuring of the human auditory cortex can be measured by a number of techniques. Huttenlocher and Dabholkar (1997) counted synapses in the post-mortem auditory cortex and found, first, an increase in the number of synapses following birth until early childhood (synaptogenesis) and, then, a decrease in the number of synapses (pruning) until adult values were reached during early adolescence. Moore and Guan (2001) examined the laminar development of auditory cortex and found differential development of axonal densities between infragranular and supragranular layers that did not reach maturity until early adolescence (Moore & Guan, 2001). Because these developmental changes are reflected in the scalp recorded auditory evoked potentials, we and others have charted long term changes in cortical development in humans using CAEPs (Albrecht et al, 2000; Cunningham et al, 2000;

Eggermont, 1988; Gilley et al, 2005; Gomes et al, 2001; Ponton et al, 1996; Ponton & Eggermont, 2001; Ponton et al, 2000; Sharma et al, 2002b; Sharma et al, 1997; Tonnquist-Uhlen et al, 2003).

#### *Auditory evoked potentials: Normal development*

Auditory evoked potentials reflect synchronized electroencephalographic (EEG) activity in response to sound. In infants and children the cortical auditory evoked response is dominated by a large positivity, the P1. P1 is seen at latencies of 100–300 ms after stimulation. As age increases, an invagination appears in the broad P1 waveform in the form of the N1 component of the CAEP. Although the N1 component can be seen in children as young as 3–5 years of age at a slow stimulation rate, it is consistently seen in children by about age 12 years at standard stimulation rates (Gilley et al, 2005). Ponton and Eggermont (2001) suggest that the surface positivity of the P1 response is consistent with ‘a relatively deep sink ([in cortical] layers IV and lower III) and a superficial current return.’ P1 generators include primary and secondary auditory areas, while the N1 likely reflects reciprocal and re-entrant auditory cortical activation as a result of intra- and inter-hemispheric activity (Makela & Hari, 1992; Makela & McEvoy, 1996; Ponton et al, 2000). 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 et al, 1991), it would be reasonable to assume that 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.

The latency of the CAEP varies with age and, thus, can be used as a biomarker for maturation of central auditory pathways (Eggermont, 1988; Wunderlich et al, 2006; Sharma et al, 1997, 2002a; Albrecht et al, 2000; Pang & Taylor, 2000; Ponton et al, 2000; Gomes et al, 2001; Onofrij et al, 2001; Gilley et al, 2005). Sharma et al (1997, 2002a) have described in detail the normal developmental trajectory of the P1 response from birth to adulthood. They examined the latency of P1 as a function of age in 190 normal hearing subjects ranging in age from 0.1 years to 20 years. The results revealed a strong negative correlation between age and latency of P1. The decrease in P1 latency with increasing age suggests more efficient synaptic transmission over time and may reflect a more refined (or pruned) auditory pathway. These normative data provide a standard against which we have charted the central development of congenitally deaf children who are fitted with cochlear implants.

#### **Abnormal development following deprivation: Congenitally deaf cats**

Given that the organization and development of cortical auditory pathways is driven, in part, by input signals, then cortical organization and development must be altered in the case of congenital deafness. Congenitally deaf white cats are a useful model system to study cortical organization following deafness and changes in cortical organization following the onset of stimulation by a cochlear implant. Most generally, congenitally deaf cats: (1) show a restricted (atypical) pattern of activation within the layers of the primary auditory cortex compared to normal-hearing cats, and (2) show signs of

desynchronized activity among different cortical layers. As a consequence, there are changes in morphology of local field potentials recorded at the cortical surface (Kral et al, 2002; Kral and Tillein, 2006; Kral et al, 2005).

When electrical stimulation is started after four 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 et al, 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, 2002, 2005; review Kral this volume). Such a decoupling may allow other sensory input to predominate in the higher order auditory cortex in children deprived of sound for a long period. Decoupling of primary cortex from higher order auditory could facilitate the recruitment of the higher order auditory cortex by other modalities such as vision (Bavelier and Neville, 2002; Lee et al, 2003) and somatosensation. We will return to this in a later section.

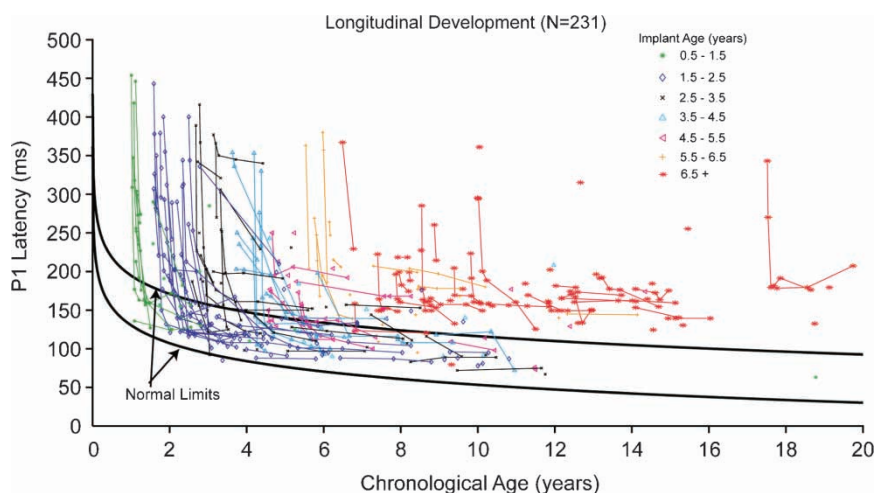
### Abnormal development following deprivation: Humans

The abnormal cortical development following deprivation detailed above should alter CAEPs recorded from deaf children fitted with a cochlear implant. Of course, we should suppose that the duration of deafness before implantation would play a

significant role in the magnitude of the changes seen in the CAEP, i.e. smaller changes in children fitted with a cochlear implant early in childhood and larger changes in children fitted later in childhood. Ponton et al (1996) first demonstrated differential CAEP development in children and adults fitted with CIs by comparing the waveform morphologies to those from normal hearing individuals. Results of that study revealed a delay in the latency of the P1 and a general absence of the N1. Sharma et al (2002b) examined P1 latency in 245 congenitally deaf children fitted 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. Individual developmental trajectories for cortical response latencies as a function of age for cochlear implanted children are shown in Figure 1. As seen in Figure 1, latencies for children implanted early were driven into the range of normal following 3–6 months of stimulation and, critically, normal changes in latency were observed over ensuing years (Sharma et al, 2005, 2002c). Children implanted late in childhood revealed latencies that changed immediately following implantation but failed to continue to change over time. 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 et al (2005).

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.

Eggermont and Ponton (2003) found that the N1 component in the CAEP was absent in cochlear-implanted subjects who had



**Figure 1.** Individual developmental trajectories for cortical response latencies in cochlear-implanted children compared to the 95% confidence intervals for normal development of P1 latency (solid lines). Response latencies for individual subjects measured at various time points after implantation are connected by a solid line.

been deaf for a period of at least three years under the age of six years. On the basis of this finding, Eggermont and Ponton (2003) suggested that this period reflects a critical time for cortical maturation and for achieving useful speech perception.

Recent data from our laboratory show that children who are implanted after age 7 years never develop an N1 response. On the other hand, children implanted before the sensitive period of 3.5 years will develop an N1 component that is similar in morphology and latency to that found in normal hearing children (Sharma & Dorman, 2006). Moreover, the emergence of the N1 component follows a normal developmental time course. Given the increased likelihood of successful speech perception in children implanted at an early age, the coincidental N1 development, whose generators include the higher-order auditory areas, may provide further insight into the relationship between early stimulation and behavioral outcomes much later in childhood.

Both our P1 and N1 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 et al, 2000, 2001; Ryugo et al, 1997) and in humans (Lee et al, 2001; Schorr et al, 2005).

### **Reorganization of the auditory cortex following deafness**

A fundamental principal of neurophysiology is that cortical areas will reorganize following a period of stimulus deprivation. That is, children who are born deaf will, at some time during childhood, likely after the end of the sensitive period, experience cortical reorganization in areas that normally respond to sound stimulation. Gilley et al (2006) recorded 64-channel EEG in normal-hearing, early implanted and late-implanted children while they listened passively to a speech sound /ba/. Current density reconstructions using standardized low resolution electro-magnetic brain tomography (sLORETA) and dipole source analyses were performed in the time frame of the P1 & N1 CAEP responses. As expected, auditory stimulation activated the superior temporal sulcus bilaterally and the right inferior temporal gyrus for normal hearing children. For early implanted children, activation was observed along the superior temporal sulcus contralateral to the implanted ear, and right inferior temporal gyrus activation independent of the ear stimulated. In addition, a minor source of activity was localized to the anterior parietotemporal cortex. Overall, early implanted children showed activation that was similar to normal hearing children. On the other hand, children implanted after the end of the sensitive period (i.e. after age 7 years) showed low amplitude, diffuse activity from the primary generators identified in the normal-hearing and early-implanted children. These late implanted children primarily showed activation of anterior parietotemporal cortex contralateral to the stimulated ear. In order to interpret these results, we first consider studies which clearly suggest that the primary auditory cortex is engaged in auditory processing in implanted persons (Lazeyras et al, 2002; Roland et al, 2001; Seghier et al, 2005). If we assume that generators of early components of the CAEP, such as the P1 and N1, include

input from intracortical and intercortical recurrent activity between primary auditory and association areas, then absence of auditory cortical activity in the late implanted children in the Gilley et al (2006) data 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.

### **Cross-modal plasticity and reorganization**

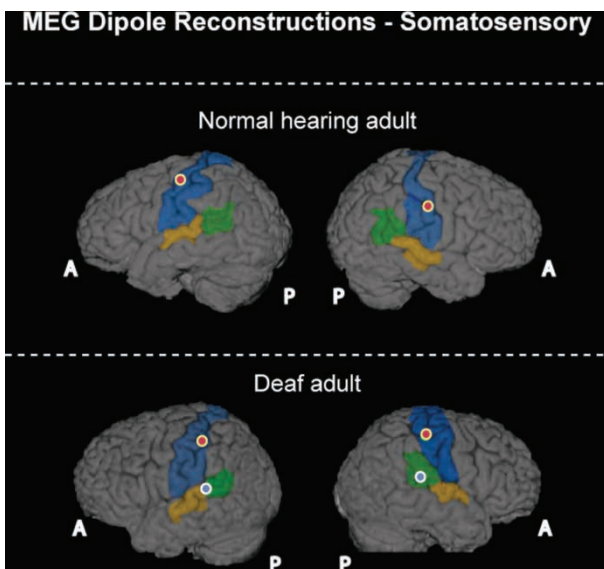
The results of the Gilley (2006) study described above suggest that auditory stimulation does not activate auditory association areas in a normal fashion in late-implanted children. Therefore, it may then be reasonable to assume that auditory association areas are engaged in processing input from other modalities. There is a long history of studies describing that auditory areas in deaf adults respond to visual stimuli (Bavelier et al, 2000, 2001; Bavelier & Neville, 2002; Armstrong et al, 2002; Fine et al, 2001; Finney et al, 2001; Fenwick et al, 1981). For example, Finney and colleagues (2001) presented visual stimuli to congenitally deaf adults and monitored brain activity using fMRI. The fMRI responses showed prominent activity in the temporal cortex in response to visual stimuli, specifically in the auditory cortical regions. Similarly, fMRI studies of deaf adults who communicate using sign language show increased activity in auditory areas in response to sign language, lip movements, and basic visual motion stimuli (MacSweeney et al, 2002; Sadato et al, 2005). For a more complete review see Mitchell (this issue).

We are examining cross-modal plasticity in deaf adults and children using somatosensory stimulation. In a study by Baldwin 2002, magnetoencephalographic (MEG) brain activity was recorded using a 306-channel magnetometer in normal hearing and deaf adults during vibrotactile stimulation to the hand. Dipole solutions were constrained using individual subjects' structural MRI scans for the analysis and three-dimensional rendering. Data from one normal hearing and one deaf adult are shown in Figure 2. Dipole source analysis of the averaged evoked potentials revealed bilateral activation of somatosensory cortex in the normal hearing adult. However, as seen in Figure 2, 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. These results suggest at least some cross-modal plasticity and reorganization between somatosensory and auditory areas is likely after auditory deprivation.

### **Reorganization and competition**

If the developing brain becomes organized in a fundamentally different manner as a consequence of auditory deprivation, how does the brain handle input from a new sensory experience when hearing is restored with a cochlear implant?

In early development, the cortex can be characterized as having exuberant neural connections (as evidenced by high synaptic



**Figure 2.** MEG dipole reconstructions for responses to somatosensory stimulation. Each dipole is shown projected to the surface of the rendered cortex using the individual subject's structural MRI scan. Shaded regions represent functional areas of the cortex: somatosensory (dark blue), auditory primary and secondary (orange), and multi-modal auditory (green). The multi-modal auditory area at the left hemisphere is traditionally associated with Wernicke's area. A = anterior, P = posterior.

densities (Bourgeois et al, 1994; Huttenlocher, 1979; Rakic et al, 1986); complex axonal arborization (Antonini and Stryker, 1993; Moore & Guan, 2001); and complex dendritic development (Mooney et al, 1992; Wallace et al, 1992; Valverde, 1968). Stimulus dependent development and pruning of these neural connections shapes the specialization of cortical sensory and multisensory areas (Quartz & Sejnowski, 1997). When sensory input is deprived during development, unstimulated pathways in the auditory cortex remain unpruned and normal dendritic arborization does not occur. Therefore, these unpruned pathways and connections between sensory and multisensory areas may provide a conduit for other modalities to access auditory areas.

If reorganization occurs during deprivation and becomes 'set' after a sensitive period for development, then introducing a new sensory input could potentially disrupt these established neural connections. That is, when CI stimulation is introduced after reorganization, the reorganized brain experiences a new competition for resources. In order to examine the functional consequences of decoupling and reorganization, Gilley et al (2006) examined reaction times to basic auditory, visual and auditory-visual (AV) stimuli in normal-hearing and cochlear-implanted children. The results revealed that late-implanted children showed delayed auditory, visual, and AV reaction times relative to early-implanted and normal-hearing children. These results are consistent with a recent study which demonstrates abnormal AV integration (McGurk effect) in late-implanted children (Schorr et al, 2005). Taken together these results suggest that in late-implanted children, input, via a cochlear implant into a reorganized cortex, may lead to a new competition for resources resulting in abnormal sensory perception skills,

atypical responses to multisensory input, and a general sluggishness of systems.

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