Cochlear Implants and Brain Plasticity

Audiology & Neuro-Otology

Audiol Neurootol 2001;6:346–362

Received: April 17, 2001
Accepted after revision: July 30, 2001

Delayed Maturation and Sensitive Periods in the Auditory Cortex

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Key Words

Hearing · Cochlear implants · Plasticity · Development · Implantation age · Congenitally deaf white cat

Abstract

Behavioral data indicate the existence of sensitive periods in the development of audition and language. Neurophysiological data demonstrate deficits in the cerebral cortex of auditory-deprived animals, mainly in reduced cochleotopy and deficits in corticocortical and corticothalamic loops. In addition to current spread in the cochlea, reduced cochleotopy leads to channel interactions after cochlear implantation. Deficits in corticocortical and corticothalamic loops interfere with normal processing of auditory activity in cortical areas. Thus, the deprived auditory cortex cannot mature normally in congenital deafness. This maturation can be achieved using auditory experience through cochlear implants. However, implantation is necessary within the sensitive period of the auditory system. The functional role of long-term potentiation and long-term depression, inhibition, cholinergic modulation and neurotrophins in auditory development and sensitive periods are discussed.

Humans use symbolic communication, language, for the exchange of information. This communication is based on intact hearing. The ability to acquire language is inborn, but language has to be learned under appropriate acoustic stimulation. Congenital hearing loss therefore strongly affects the development of language competence. This development takes place in sensitive periods, i.e. age spans in which the nervous system requires external stimulation to develop competence for processing the inputs. Deprivation often results in a nonfunctional neural system. The present review is focused on the cortical nervous processes taking place after early and late cochlear implantation in congenitally deaf patients. First, we will review evidence for behavioral deficits following congenital deprivation of the audition-language system, secondly the functional neural processes taking place in primary and higher-order cortical areas in congenital deprivation and cochlear implantation will be addressed.

Behavioral Deficits in Congenital Deprivation

Behavioral manifestations for sensitive periods can be found both in language-deprived and auditorily deprived children.

Language Deprivation and Language Development

Language is a human-specific phenomenon [Pinker, 1994]. The cortical areas involved in language processing (here called language system) have been identified by case reports and electrical stimulation of the cortex in unanes-

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thetized humans [review in Ojemann, 1991] and functional imaging [review in Price, 2000; Giraud et al., 2001, this issue]. The basis of language is innate, but experience is necessary to develop a fully competent language system [Chomsky, 1959; Bickerton, 1990] and a sensitive period in the development of language has been proposed [review in Lenneberg, 1967]. This view has been supported by data gained from 'wild children' who lived in a language-deprived environment for a prolonged time and, despite normal hearing, failed to learn language subsequently [Curtiss, 1977]. A critical analysis of these few case reports substantiated the notion that a sensitive period exists. It has been estimated to last until approximately 7 years after birth [review in Skuse, 1993]. Yet, there are caveats with respect to the above reports: (1) An accompanying mental retardation causing language learning problems cannot be excluded. (2) Language deprivation is accompanied by social deprivation. Lack of social contacts has substantial influence on language development.

Conductive Hearing Loss and Language Development

Language consists of several subsystems with different developmental periods [Neville et al., 1992]. Phonological perception matures during the first 8–10 months of life [Werker et al., 1981], basic semantic abilities during the first 2–4 years and syntactic abilities mature over a longer period and are fully developed by the age of 15 years. Language and speech has been analyzed in children with early middle-ear infections [review in Ruben, 1997, also Bishop and Mogford, 1993]. The results show that several aspects of language are affected irreversibly if hearing is impaired during the given developmental period [Ruben, 1997]. Unfortunately, it is difficult to differentiate between deficits in the language system, its input synapses and the main input system – the auditory system. Do these findings also indicate the existence of sensitive periods in the phonological subsystem and/or the auditory system? This needs to be discussed with regard to data from the congenitally deprived auditory cortex.

Auditory Deprivation and Language Development

Undiagnosed congenitally deaf children living in normal social surroundings develop a rudimentary sign language [home-sign, Goldin-Meadow and Mylander, 1990; Grimshaw et al., 1998], without explicit teaching by parents or teachers. Apparently, in a normal social environment congenitally deaf children can also exploit nonverbal means of communication. The neural mechanism responsible for this development is unknown, but there are data on cortical neural activity in long-term users of American Sign Language. In these people the language system is activated by visually presented signs in a similar manner to that of hearing subjects by speech [Neville et al., 1998; Nishimura et al., 1999; Petitto et al., 2000]. Many language areas are multimodal and receive projections from both visual and auditory systems at least [Pandya and Yaterian, 1985; Weeks et al., 2000; Petitto et al., 2000]. Multimodal areas are capable of great cross-modal compensatory plasticity [review in Rauschecker, 1995]. Abolishment of sound-evoked activity in the auditory system of congenitally deaf people may favor synaptic connections from the visual system to the cortical areas for language and can lead to the suppression of projections from the auditory system. Consequently, late implantation of cochlear implants may result in insufficient activation of the language areas for production and analysis of speech signals.

Congenitally Deaf Patients with Cochlear Implants

Cochlear implants are useful tools to provide auditory sensations in profoundly deaf patients [review in Rubinstein and Miller, 1999]. Although the electrical stimulation only poorly represents the cochlear place information [Hartmann et al., 1984; van den Honert and Stypulkowski, 1987; Kral et al., 1998], temporal information is reliably represented [Hartmann et al., 1984; van den Honert and Stypulkowski, 1984; Knauth et al., 1994; Shepherd and Javel, 1997, 1999; Javel and Shepherd, 2000]. This is obviously sufficient for frequency discrimination over lower frequencies and thus makes speech comprehension possible [Sachs, 1984; Kral and Majernik, 1996; Langner, 1997; Moller, 1999; Kral, 2000].

In congenitally deaf children, cochlear implants enable language development, but the outcome is critically dependent on the age of implantation [Busby et al., 1992, 1993; Manrique et al., 1995; Zwolan et al., 1996; Tyler et al., 1997; Busby and Clark, 1999; Kiefer et al., 1999]. Congenitally deaf subjects implanted in adulthood showed a markedly poorer performance in speech discrimination than subjects implanted in childhood. As a consequence, screening programs of neonatal or early postnatal hearing status are being introduced in several countries [NIH Consensus Statement, 1993, 1995; Lutman and Grandori, 1999]. According to present guide-

lines, the optimal implantation age is under 5 years [Fryauf-Bertschy et al., 1997] in congenitally deaf subjects. Some authors suggest that implantations should be performed before the end of the 2nd year of life [O'Donoghue, 1996, 1999; Klinke et al., 2001]. What are the reasons for sensitive periods and which neural processes take place during these periods? Can cochlear implantation play the role of an external trigger for language acquisition?

Neurophysiology of Sensitive Periods in the Auditory Cortex

Like the language system, the auditory system also undergoes developmental changes during early postnatal life in both humans and animals [review in Romand, 1992; comparison cat – human in Ponton et al., 1999]. In the cat, functional cortical electrophysiological parameters in the primary auditory cortex mature during the first 5 months [Eggermont, 1996]; in man, during the first 12–15 years [Eggermont, 1988]. As is the case with language, postnatal development of the auditory system is dependent on experience. The maturation process cannot proceed under congenital auditory deprivation.

Auditory Deprivation and Higher-Order Auditory Cortex

Cats which have been binocularly deprived from birth (suture of eyelids) have been shown to be superior in auditory localization tasks than sighted cats [Korte and Rauschecker, 1993; Rauschecker and Korte, 1993]. This result indicates sensory substitution for blindness. A functional correlate for this phenomenon was found in the anterior ectosylvian auditory area, a higher-order auditory area adjoining the anterior auditory field and secondary auditory area AII [Rauschecker, 1995]. Not only were the units in this area more sharply tuned to spatial location, but the auditory area also expanded into regions devoted to visual stimuli in sighted cats [Rauschecker and Korte, 1993]. Under similar experimental paradigms with neonatal eyelid suture or bilateral enucleation, the units responsive to acoustic stimuli in secondary and primary visual areas have been investigated [Yaka et al., 1999]. Cross-modal remapping was demonstrated in higher-order visual areas (anterolateral lateral suprasylvian and anteromedial lateral suprasylvian area). However, only few units responded to auditory stimulation in the primary visual cortex [Yaka et al., 1999]. In humans, higher-order sensory areas are also capable of cross-modal remapping [visual human: Röder et al., 1996; Cohen et al., 1997; Lessard et al., 1998; Weeks et al., 2000; review Giraud et al., 2001, this vol.]. Consequently, the inputs to deprived secondary sensory areas are possibly replaced by inputs from another sensory system.

The higher-order auditory cortex (e.g. AII in cats) has greater physiological plasticity than the primary auditory cortex [Diamond and Weinberger, 1984; Weinberger et al., 1984]. In congenital auditory deprivation, the higher-order auditory cortex may be recruited for the processing of other sensory modalities. This view has been supported by the observation that performance of deaf patients in visual and cognitive tests is better than in hearing subjects [Neville and Lawson, 1987a, b; Levänen et al., 1998; Marschark, 1998; Parasnis, 1998].

Experimental evidence for cross-modal remapping of the human auditory cortex has recently been presented. Higher-order auditory areas, but not the primary auditory cortex, are incorporated in processing of visual stimuli (visually presented signs) in humans [Nishimura et al., 1999; Petitto et al., 2000]. In prelingually deaf patients, the amount of activation of the higher-order auditory cortices by a cochlear implant decreases with increasing implantation age [Lee et al., 2001]. Speech recognition by a cochlear implant correlates significantly with the activation in higher-order auditory cortices [Lee et al., 2001]. Thus, cross-modal remapping of the higher-order auditory cortices may substantially interfere with speech processing after cochlear implantation.

Auditory Deprivation and Primary Auditory Cortex

Congenitally deaf patients implanted in adulthood show deficits in temporal auditory processing such as gap detection and auditory counting abilities [Busby et al., 1992, 1993; Busby and Clark, 1999], which indicates a malfunction of the central auditory system. This is at least one of the causes of speech-processing difficulties experienced by congenitally deaf patients implanted as adults.

Several laboratories have investigated the neural basis of reduced auditory performance in deaf animals using different models. Unfortunately, complete auditory deprivation is more difficult to achieve than visual deprivation. Simple ear plugging leads to hearing loss of around 40 dB, under special circumstances 70 dB [Nixon and van Gierke, 1959; Samson et al., 1994]; bone conduction and vocalizations, breathing, chewing, etc. are not attenuated

at all. Nonetheless, even with this type of conductive hearing loss, impairment in binaural processing has been demonstrated [Samson et al., 1994].

For critical evaluation of auditory deprivation experiments it is necessary to discuss the relevant deafness models. Only models for neonatal deafness will be considered.

Deafness Models

Cochlear Ablation. The cochlea is postnatally ablated [Kitzes et al., 1995; Russell and Moore, 1999; Gabriele et al., 2000]. Such animals have been used to investigate effects of monaural deprivation. The possible drawbacks of this model are: (a) Functional data cannot be gained at the ablated side. Electrical stimulation through a cochlear implant is not possible. (b) Ablating the cochlea also interrupts a possible trophic pathway from the cochlea to the brainstem. Deficits found in cochlea-ablated animals might therefore be related to a complete loss of potential cochlear growth- and neurotrophic factors. Extensive subcortical cross-modal reorganization following ablations in the central auditory system [review in Wakita and Watanabe, 1997] is not found in spontaneous congenital cochlear degeneration [Hartmann et al., 1997; Heid et al., 1997]. (c) The spontaneous activity in the cochlea is perfectly normal until ablation. Spontaneous activity has a shaping influence on the maturing sensory system [for visual system see Stryker and Harris, 1986; review in Wong, 1999]. The advantages of this model are: (a) doubtless total hearing loss, and (b) no restrictions in numbers of animals available.

Pharmacological Neonatal Deafening Using Ototoxic Substances [Leake-Jones et al., 1982; Xu et al., 1993; Shepherd and Martin, 1995]. Possible drawbacks are: (a) The substances used in these models have a direct effect on the myelin sheath and the spiral ganglion cells [Hardie and Shepherd, 1999]. The animals loose 50–90% of spiral ganglion cells [Leake et al., 1999]. Electrical stimulation using cochlear implants can yield variable activation of the auditory system depending on the survival of primary afferents. Some phenomena may be obscured by large variability of the results. These effects can be reduced by using a relative criterion for stimulation (e.g. behavioral thresholds or thresholds of the electrically evoked brainstem responses) [see Beitel et al., 2000]. (b) The spontaneous activity until deafening is normal. Advantages of the model: (a) Doubtless total hearing loss if high doses are applied. (b) No restrictions in the numbers of animals available.

Congenital Hearing Loss. 'Congenitally deaf cats' are selected and bred [Bosher and Hallpike, 1965; Saada et al., 1996; Heid et al., 1997, 1998; Ryugo et al., 1998]. Possible drawbacks of congenitally deaf animals are: (a) Unknown spontaneous activity in the auditory nerve in prenatal and postnatal period. So far only data on adult cats have been presented [Ryugo et al., 1998]. (b) Deafness of the individual animals has to be verified at an early age (3rd and 4th week) in order to exclude some early hearing experience [Heid et al., 1998]. (c) The animals are not easily available. Advantages of the model: (a) Similarity to human Scheibe dysplasia, the closest model to major types of human congenital deafness [Mair, 1973; Ryugo et al., 1998]. (b) Good preservation of cochlear afferents in animals younger than 2 years [Hartmann et al., 1997; Heid et al., 1998]. The slow degeneration in the auditory nerve of congenitally deaf cats corresponds to human auditory nerve fiber degeneration, which has also been described as a slow process [Felix and Hoffmann, 1985; Felix et al., 1990; Vasama and Linthicum, 2000].

Monaurally Deprived Auditory Cortex

The auditory cortex of unilaterally deprived cats was investigated by Reale et al. [1987]. Unilaterally neonatally cochlear-ablated cats were used in the study. At the age of 6 months and above (which is nearly adult for cats) multiunit responses in middle cortical layers (layer III/IV) indicated that the primary auditory cortex ipsilateral to the hearing ear was more responsive to the stimulation when compared to control cats [compare also Middlebrooks et al., 1980; monkey: Reser et al., 2000]. Subcortical reorganization has been shown in the auditory system of these cats, which corresponds to the functional and morphological findings in ferrets and guinea pigs after unilateral cochlear ablation [Kitzes and Semple, 1985; Moore and Kitzes, 1985; Moore et al., 1993; Kitzes et al., 1995; Russell and Moore, 1995]. Such subcortical changes could substantially contribute to the reorganization of the ipsilateral cortex. Possible mechanisms of the reorganization are rapid disinhibition or true plastic reorganization with accompanying morphological changes. The ipsilateral responses might also have arisen from the reorganization of interhemispheric corticocortical projections.

McMullen et al. [1988] showed that unilateral neonatal deafening leads to dendritic reorganization of spiny-free neurons in the contralateral auditory cortex of the rabbit; no changes were found in spiny dendrites. Nonspiny dendrite length increased by 27% relative to littermate controls, preferentially in a tangential direction. An increase in the span of the dendritic arbors of cortical neurons can

participate in the functional reorganizations demonstrated by Reale et al. [1987]. Neonatally deafened rabbits have 38.7% fewer spines along their basal dendrites in the primary auditory cortex [McMullen and Glaser, 1988], indicating a loss of synapses after deprivation. However, different species have been used in these studies, so that direct correlations cannot be made.

In conclusion, monaural deprivation leads to substantial reorganization of both the subcortical projections and the cortical activation patterns. The hearing ear, at least in cochlear ablation, activates the ipsilateral auditory structures and cortex more efficiently. The finding is supported by increased projections of the hearing ear to ipsilateral auditory nuclei and primary auditory cortex. These projections may possibly replace projections from the ablated cochlea. Part of the functional changes seems to be due to dendritic rearrangements in the primary auditory cortex.

In the visual system, neonatal monocular deprivation leads to rearrangement of the response characteristics, where the functional eye recruits the units normally responsive to the occluded eye [Hubel and Wiesel, 1970; Fregnac and Imbert, 1984; Horton and Hocking, 1997]. Despite substantial differences in the functional organization of the auditory and visual systems, these data seem to correspond well. In addition, a sensitive period of 3–5 months has been demonstrated for monocular manipulations in cats [review in Blakemore, 1975; Fregnac and Imbert, 1984]. In humans, surgical intervention in congenital strabismus is recommended before the beginning of the 4th year of life [Epelbaum et al., 1993], but earlier treatment even within this time is more effective [Birch and Stager, 1996].

Binaurally Deprived Auditory Cortex

Binaural deprivation was studied in pharmacologically deafened or congenitally deaf cats. The auditory system was stimulated electrically through a cochlear implant. In order to define deficits in the auditory cortex of these animals, data were compared to electrically evoked responses in hearing cats (i.e. with normally developed auditory systems) deafened (in the majority of studies) at the beginning of the experiment.

Cortical responses to electrical intracochlear stimulation of the auditory nerve were first described by Raggio and Schreiner [1994] and Popelar et al. [1995]. These studies were undertaken on normal-hearing cats. Thus, a normally developed auditory system processed an unfamiliar stimulus. The data showed that electrical stimulation activates the auditory cortex in a cochleotopic manner. The temporal properties of neurons were similar to acoustically driven responses, the temporal resolution being better with electrical stimulation [Schreiner and Raggio, 1996]. The rate-level and latency-level functions were also similar [Raggio and Schreiner, 1994]. Differences in rate-intensity functions, such as monotonic or nonmonotonic functions, could be observed between the different stimulation modes for different neurons.

Deprivation effects in the central auditory system involving the auditory brainstem have been shown by numerous authors [review Shepherd et al., 2001, this vol.]. Cortical responses were studied by Hartmann et al. [1997] in congenitally deaf cats. The authors recorded electrically evoked field potentials and single and multiunits from the auditory cortex of adult specimens that had never gained hearing experience. The study showed that the naive auditory cortex can be activated even in adult congenitally deaf animals. Furthermore, a rudimentary cochleotopic representation was found within AI. Earlier PET data on human subjects [Truy et al., 1995] were therefore confirmed. Single units in cats displayed a short latency response to pulsatile stimulation (shortest latency 8 ms) with a successive suppression of spontaneous activity. The latencies were as in normal-hearing cats with electrical stimulation [Raggio and Schreiner, 1994]. Rudimentary cochleotopy has been partially confirmed in neonatally deafened animals [Raggio and Schreiner, 1999]. Based on single- and multiunit recordings in middle cortical layers cochleotopical organization was reported in ventral parts of the AI field despite short-term deafness, but in the dorsal part of AI this cochleotopy was considerably blurred. In long-term deafness, these animals maintained only weak or no signs of cochleotopy. In addition, Raggio and Schreiner [1999] demonstrated two regions of lower thresholds separated by a high-threshold ridge in the auditory cortex, which correspond to two cortical high-amplitude spots in field-potential recordings of congenitally deaf cats [Klinke et al., 1999; Kral et al., 2001, compare electrical stimulation in hearing cats in Volkov and Dembnovetskii, 1979; Raggio and Schreiner, 1994; Popelar et al., 1995; Schreiner and Raggio, 1996]. However, a significant loss of primary afferents in neonatally deafened cats, especially in long-term deafness, represents a confounding factor which is unavoidable. Raggio and Schreiner [1999] discussed reduced inhibition in short- and long-term deaf animals as a possible cause of reduced cochleotopy. Reduced inhibition, resulting in reduced cortical cochleotopy, may be an additional reason for unwanted channel interactions complicating speech understanding in implanted patients.

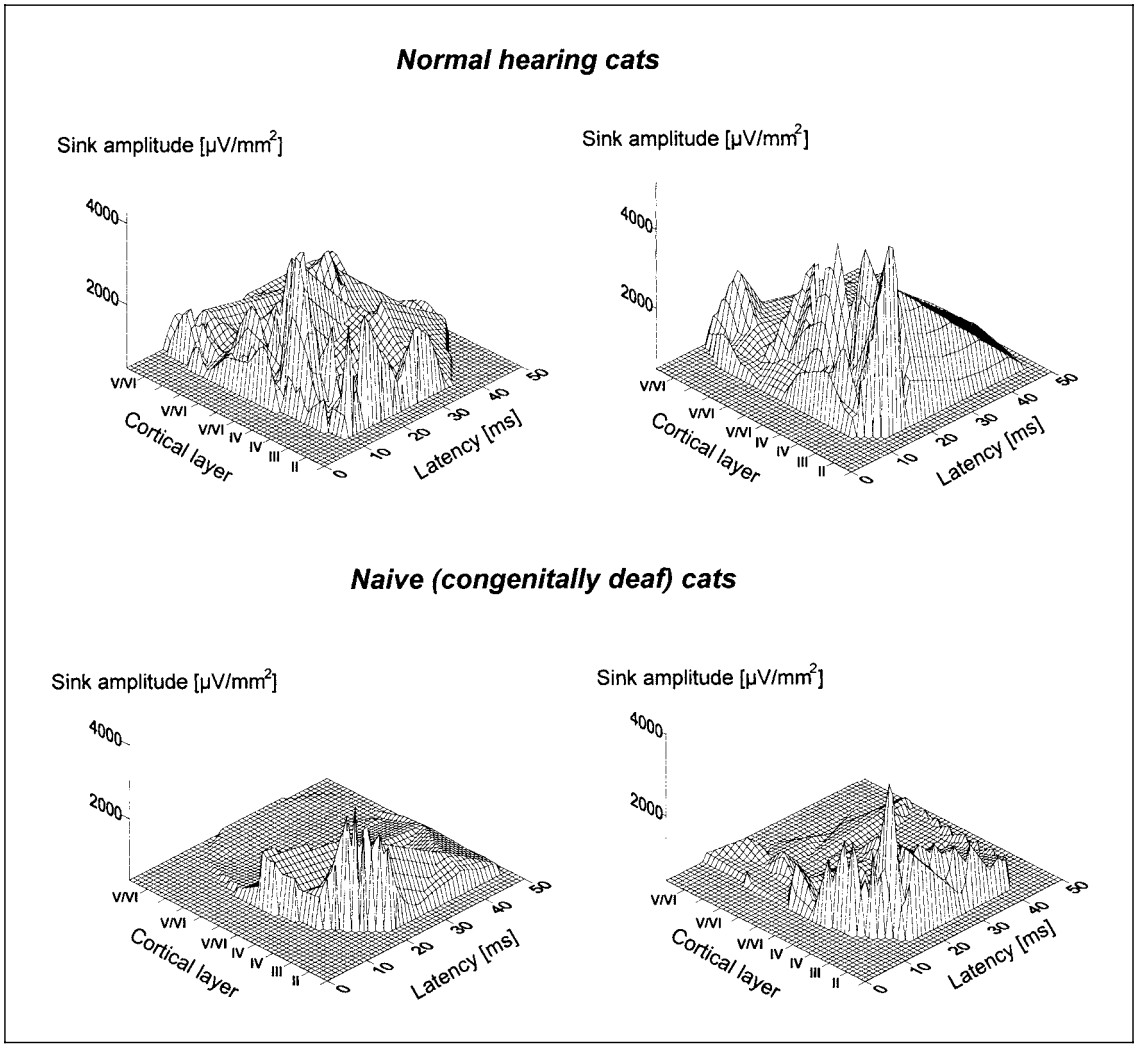


Fig. 1. Maximum sink amplitudes as evaluated from 6 penetration tracks at the region of maximum field potential amplitudes in the primary auditory cortex. Maximum sink amplitudes correspond to maximum synaptic currents in the given cortical layer and latency. Normal cats have significantly higher sink amplitudes and more synaptic activity in infragranular layers and at longer latencies (>30 ms). Modified from Kral et al. [2000].

Most studies on the cerebral cortex, including plasticity studies, have been carried out in the 'middle cortical layers' III/IV. However, cortical layers differ in their plasticity when adult animals are compared to young ones, and layer III remains plastic well into adulthood [Singer, 1995; review in Kaczamrek et al., 1997]. The effects of deprivation should therefore be investigated in all cortical layers. Pronounced functional deficits in primary auditory cortices of congenitally deaf animals have been observed when activity was evaluated in a layer-specific manner [Kral et al., 2000]. Current source densities were computed from field potentials recorded in different cortical layers. This technique provides measures of synaptic currents [review in Mitzdorf, 1985]. Latencies of synaptic activity in different cortical layers of normal-hearing cats evoked by cochlear electrostimulation revealed direct thalamocortical activation of at least layers III, IV, V and VI, with subsequent synaptic activity in supragranular layers, followed by activity in infragranular layers [Kral et al., 2000]. Synaptic currents from naive congenitally deaf cats were significantly different from hearing cats, both in amplitude of the responses and in their spatiotemporal pattern (fig. 1). Supragranular layers (II and III) showed less synaptic activity than in hearing animals. Earliest

synaptic currents had longer latencies in naive animals than in hearing cats. Hardly any responses were recorded with latencies above 30 ms. In infragranular layers, only little synaptic activity was found in naive animals. There was a general decrease in mean sink amplitudes in naive animals [Kral et al., 2000] that corresponds to the decrease in dendritic spines reported in monocularly deprived rabbits [McMullen and Glaser, 1988].

Little synaptic activity in infragranular cortical layers implies deficits in projections into subcortical structures, most importantly to the thalamus (layer VI) [Wong and Kelly, 1981; Mitani and Shimokouchi, 1985; de Venecia et al., 1998]. Such corticothalamocortical loops may be involved in short-term memory [review in Edeline, 1999; Steriade, 1999]. Projections to more centrifugal nuclei seem also affected: layer V is the source of afferent projections to the inferior colliculus [Andersen et al., 1980; Mitani et al., 1983; for further details see discussion in Kral et al., 2000]. Unfortunately, clear differentiation between layers V and VI was methodologically difficult in the study by Kral et al. [2000]. Low synaptic activity 30 ms poststimulus also indicates functional impairments in corticocortical projections [Winguth and Winer, 1986] and possibly also in corticocortical interactions. Consequently, the highly coordinated action of the primary auditory cortex with other cortical and subcortical centers seems to be seriously disrupted after auditory deprivation. Interestingly, the development of the cerebral cortex of cats starts with infragranular layers [Friauf and Shatz, 1991; Friauf et al., 1990], and these are the first to become mature, also in humans [Huttenlocher and Dabholkar, 1997]. That might explain why they are most affected by deprivation.

Data indicating that the auditory system remains in an immature state in deaf humans too have been presented by Ponton et al. [1996] using cortical evoked potentials.

The findings can be summarized: There is a significant decrease in synaptic activity in the primary auditory cortex of naive (binaurally deprived) cats. There is a weak cochleotopic organization. The decrease in synaptic activation is layer-specific, with most pronounced decreases in infragranular (output) cortical layers and at longer latencies (>30 ms). These findings indicate that efferent projections of the primary auditory cortex to subcortical structures and possibly also to higher-order cortical areas are probably substantially diminished.

No Cross-Modal Reorganization of the Primary Auditory Cortex in Congenital Deprivation

What happens to the inactive auditory cortex in auditory-deprived animals? Cross-modal reorganization of the primary auditory cortex in these animals has been investigated by several authors. Rebillard et al. [1977, 1980] described visually evoked responses in the primary auditory cortex in congenitally deaf cats. The authors reported longer latencies indicative of higher-order sensory processing. However, these data could not be confirmed by Hartmann et al. [1997]. In this latter study, the visually evoked field potentials recorded over the auditory cortex were as small as those over other nonvisual areas and were explained by passive volume conductance. Furthermore, somatosensory stimuli did not evoke larger field potentials in the auditory cortex. Preliminary results of a subsequent study recording multiunit responses in the auditory cortex of congenitally deaf animals showed no visually evoked activity in the primary auditory cortex with either flashes or phase-reversal gratings of different orientations [Kral, Schröder, Klinke and Engel, unpubl. data]. Moreover, the primary visual cortex does not show significant cross-modal reorganization in congenital blindness in cats or humans [Yaka et al., 1999; Weeks et al., 2000].

Cochlear Implantation Induces Maturation of Auditory Cortex

To test for reversibility of the central deficits demonstrated in naive (congenitally deaf, deafened) animals, a model using chronic electrostimulation through a cochlear implant was made available for deaf animals:

For chronic electrostimulation with biologically meaningful stimuli, a portable signal processor was developed [compare Burian et al., 1979]. Klinke et al. [1999] showed that using such a stimulation system auditory experience over several months is provided for congenitally deaf cats. Pinna reflexes to auditory stimuli were used for setting stimulation currents [compare Ehret, 1985; Populin and Yin, 1998]. These reflexes are inborn and functional in most congenitally deaf cats, independent of auditory experience [Klinke et al., 1999]. The implanted animals were further classically conditioned to sounds and raised in an acoustically enriched environment, e.g. with toys making sounds when moved. Stimulation periods were from 2 to 6 months after implantation.

Field potentials recorded under controlled anesthesia [Kral et al., 1999] from the exposed primary auditory cortex after several months of auditory experience had larger amplitudes and contained long-latency responses (latency >150 ms) rarely seen in naive deaf cats. This long-latency response has previously been described in the auditory cortex of hearing cats [see Eggermont, 1992; Dinse et al., 1997]. It appears later in development than middle-latency responses [cat: König et al., 1972; monkey: Auther and

Hackett, 2001]. This fact indicates that auditory experience is important for the development of long-latency responses.

Long-latency responses have also been found in multi- and single-unit recordings in the auditory cortex of chronically electrostimulated animals [Klinke et al., 1999]. The rate-intensity functions of single units in the cortex of naive animals in response to biphasic electric pulses corresponded to rate-intensity functions recorded in the auditory nerve (fig. 2a) [Hartmann et al., 1984]. In chronically stimulated animals single-unit rate-intensity functions in the cortex were less uniform, including nonmonotonic functions (fig. 2b). At 10 dB above threshold, the poststimulus time histograms of 43% of the units demonstrated long-latency responses and more complex response types. Figure 2b shows a unit with an onset response followed by a suppression of firing and subsequent ongoing activity up to 300 ms poststimulus. Units with a very narrow long-latency peak in poststimulus time histograms have also been found [compare Klinke et al., 1999]. The more complex and less uniform response characteristics in chronically stimulated cats indicate more complex cortical processing of input activity in the chronically stimulated animals.

The origin and function of the long-latency responses have been investigated in several studies. They are possibly mediated by corticothalamic loops [Contreras et al., 1996; Steriade 1997; auditory cortex: Cotillon and Edeline, 2000] on the basis of inhibitory rebound [Eggermont, 1992]. Corticothalamic loops could be essential for short-term memory [Steriade, 1999] and also for subsequent processing in the higher-order cortical auditory areas, as the primary auditory cortex has reciprocal connections with higher-order auditory areas. Higher-order auditory areas in turn project to cortical cross-modal areas [Pandya and Yeterian, 1985]. Deficits in the functionality of thamalocorticothalamic loops can therefore affect activity in higher-order cortical areas and auditory short-term memory. Maturation of the long-latency responses is therefore of crucial importance for auditory cognitive functions. In addition to missing long-latency responses in the binaurally deprived auditory cortex, most pronounced deficits have been described in infragranular layers [Kral et al., 2000], a source of corticothalamic projections. Taken together, these data provide strong additional evidence for deficits in corticothalamic loops in congenitally deaf cats.

Current source density analyses in chronically stimulated animals [Klinke et al., 1999] indicate synaptic activation of infragranular layers comparable to normal-hearing cats. This suggests that a maturation of the auditory cortex takes place under electrical stimulation. The largest increases in synaptic currents were found in supragranular layers II/III [Klinke et al., 1999], where cortical plasticity is greatest [Kaczmarek et al., 1997]. These current-source density analyses showed a nearly normal activation of the primary auditory cortex in chronically stimulated animals. To a certain extent, the auditory cortex can obviously achieve experience-dependent maturation under electrical stimulation through a cochlear implant.

In patients, Eggermont et al. [1997] presented comparable data on long-latency responses: in implanted children these were prolonged latencies of early responses (P_1 wave) and small long-latency responses (P_2 wave) in electrically evoked potentials. These authors also reported that chronic electrostimulation through a cochlear implant approaches normalization of the evoked potentials. Early implanted children can thus catch up in maturation of the auditory system.

Cortical Developmental Plasticity Is Dependent on Age

Concomitant with the increase in response amplitudes of field potentials following long-term electrostimulation there was an expansion of the activated cortical area [Klinke et al., 1999]. The activated cortical area was defined as the cortical region showing middle-latency (10 to 50 ms) responses above 300 μV with stimulation at 10 dB above the lowest cortical threshold. This region expanded substantially with increasing duration of auditory experience. The region with large long-latency responses in the field potentials also expanded. The largest long-latency responses were found at roughly the same cortical position as large middle-latency responses.

The underlying mechanisms of expansions of activated areas in chronically electrically stimulated animals have not been elucidated yet. Considering the long time course and the substantial extent of the expansions of cortical maps in the early implanted animals, two mechanisms may be involved in plasticity:

(a) Several smaller cochleotopic reorganizations in the subcortical structures of the auditory system [review in Shepherd and Hardie, 2001, this vol.] which in sum yield a large expansion in cortical representation [compare Jones, 2000]. However, suppression of the somatosensory cortex leads to immediate expansions of neuronal receptive fields in the ventroposterior thalamus [Ergenzinger et al., 1998; compare Florence et al., 2000]. The reorganization of subcortical maps can thus be a mere top-down effect of cortical reorganization.

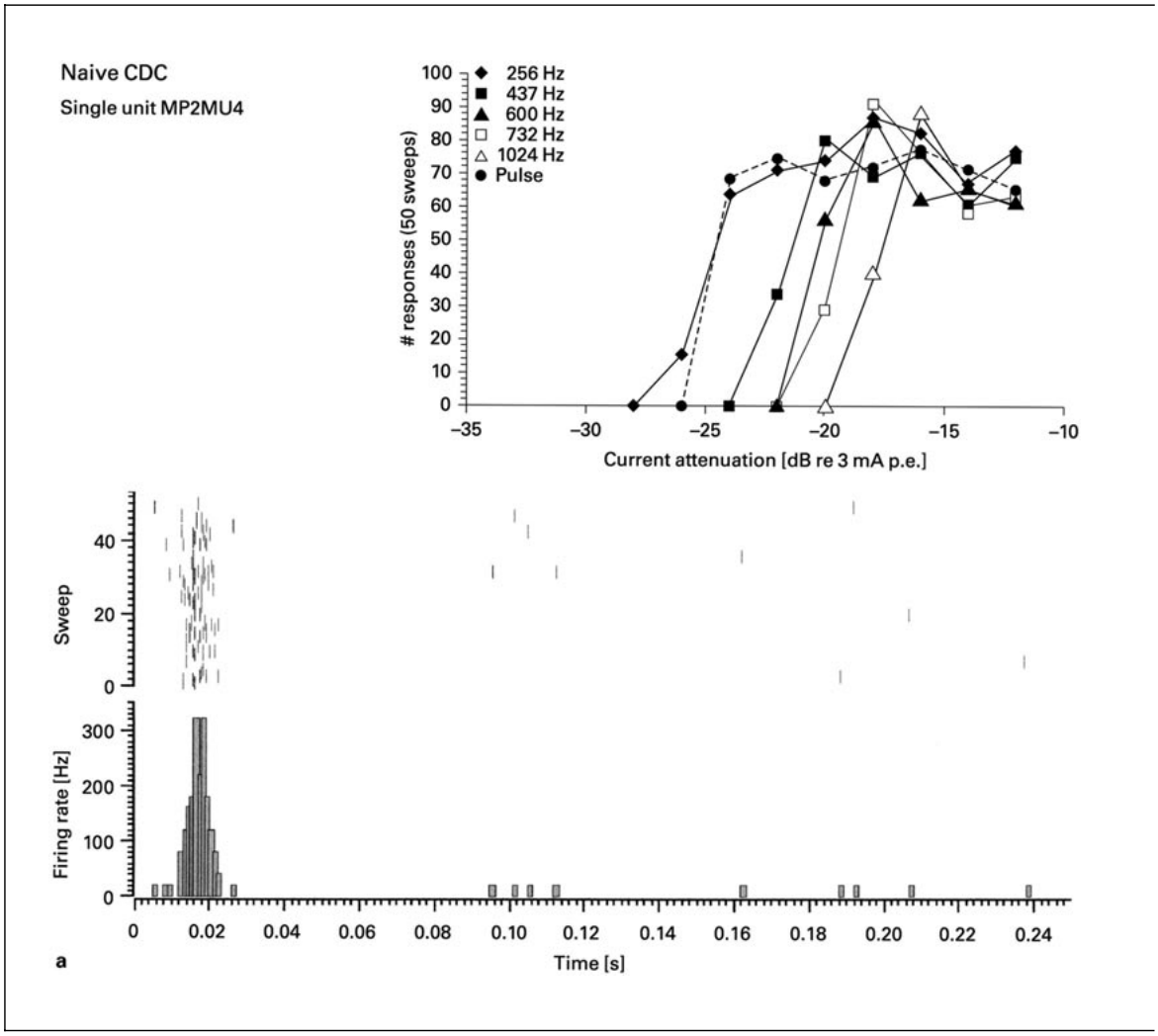
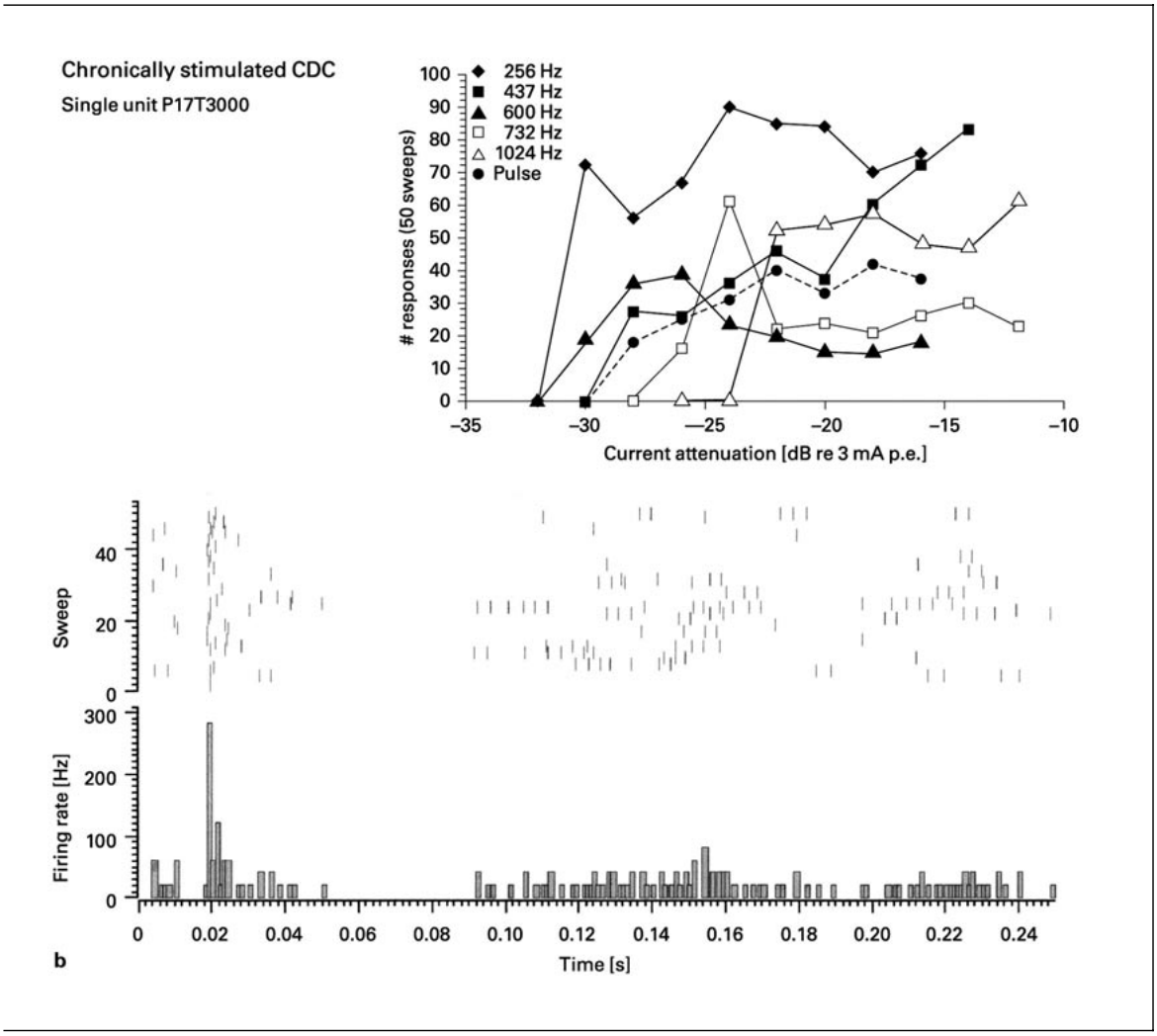


Fig. 2. Single-unit responses recorded from the auditory cortex of adult congenitally deaf cats (CDC). **a** Naive animal. Saturating rate-intensity functions of a cortical single unit for sinusoidal electrical stimuli (6 ms duration, 1 ms on/off) and biphasic pulses (200 μs/phase). Below: Poststimulus time histogram for the same unit with pulsatile stimulation at 10 dB over threshold shows a simple onset response. **b** A chronically stimulated animal, implantation age 5 months, stimulation duration 5 months. Rate-intensity functions were more complex and poststimulus time histogram revealed long-latency activity. Details in Klinke et al. [1999].

(b) A substantial expansion mainly of the thalamocortical projections and/or in corticocortical connections caused by enlargement of dendritic trees or axonal sprouting in the auditory cortex.

These expansions seem to reflect the basic functional plasticity of the cerebral cortex, as described after lesions in somatosensory, visual and motor systems. They are also a consequence of learning [reviews in Kaas, 1991; Buonomano and Merzenich, 1998]. Expansions of biologically more significant or more often utilized cortical representations have also been reported in the auditory cortex [Robertson and Irvine, 1989; Irvine and Robertson, 1990; Irvine and Rajan, 1993; Recanzone et al., 1993; Weinberger, 1998; Rauschecker, 1999; Ohl and Scheich, 1997; Pantev and Lutkenhoner, 2000].

Expansions of the activated areas can be used as a measure of cortical plasticity and the reorganization capability of the auditory cortex. Using such an approach, 7 animals were implanted at different ages [Kral et al., 2001] and the cortical activated areas were compared. Such acti-



vated areas increased up to the implantation age of 5 months. Afterwards, variability in the results increased and the activated areas were smaller (fig. 3), indicating less plasticity after late implantation. The data therefore support the hypothesis of a sensitive period in the auditory system. The areas activated on the ipsilateral cortex showed a stronger dependence on the implantation age, indicating that the amount of neural activity reaching the auditory cortex is of importance in the delimitation of the sensitive period.

The above data correspond to some earlier findings. A high-frequency hearing loss due to administration of ototoxic agents leads to larger reorganization in the auditory cortex of cats if the cochlear hearing loss takes place neonatally [Harrison et al., 1991]. The duration of the sensitive period of 5 months in cats discussed here correlates with the time of functional maturation of the cat auditory cortex, ending with the 5th month of life [Eggermont, 1996]. In humans, the morphological development of auditory cortex is characterized by two phases: (1) rapid synaptogenesis, which is genetically determined (up to 1 year postnatally), and (2) slow synaptic maturation (stabilization or elimination – 'pruning'), when almost 50% of the synapses disappear. This phase takes place from the 2nd year of life till adolescence [Conel, 1939–1967; auditory cortex, Huttenlocher and Dabholkar, 1997; in cat visual system 3–4 months p.n., Cragg, 1975a, b; Winfield, 1981]. This phase is most probably dependent on experience [compare Changeux and Danchin, 1976; Changeux and Dehaene, 1989; for birds see Wallhäuser and Scheich, 1987].

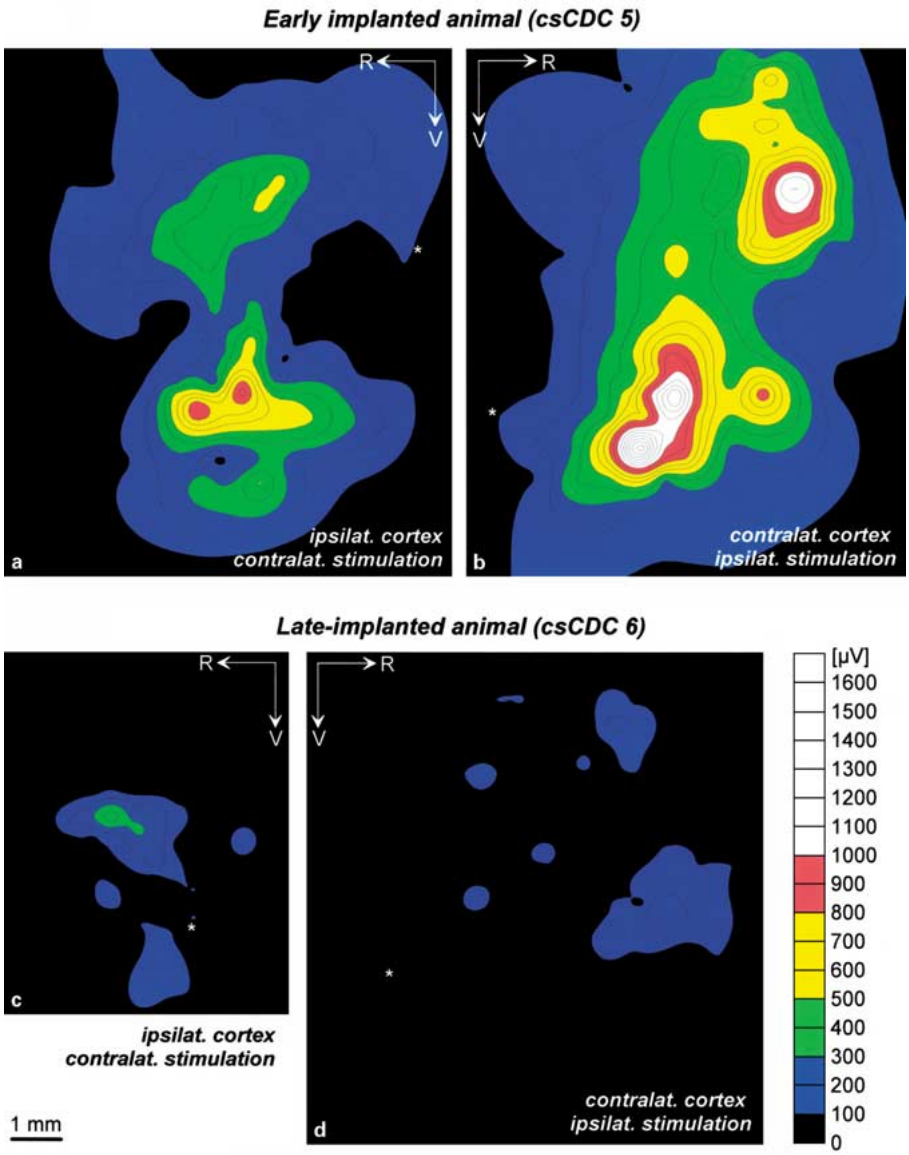


Fig. 3. Cortical activation maps obtained from 150 middle-latency responses recorded at different positions of the primary auditory cortex (500-µm grid). Stimulation: biphasic pulse (200 µs/phase) 10 dB over threshold. The animals shown had identical cortical and brainstem evoked response threshold. Shown are color-coded amplitudes. **a**, **b** Congenitally deaf cat implanted at 3.5 months and stimulated for 5 months. Shown are ipsilateral (ipsilateral to the 'trained' ear, **a**) and contralateral (**b**) cortical responses. Stimulation through the cochlear implant was at the 'untrained' ear (contralateral ear) in **a** and at the 'trained' ear (ipsilateral ear) in **b**. **c**, **d** Same recordings for a congenitally deaf cat implanted at the age of 6 months and stimulated for 5 months. The late implanted animal showed smaller amplitudes of local field potentials without long-latency responses. However, late-implanted animals showed large interindividual variability of amplitudes at the contralateral cortex. Ipsilateral responses were of consistently small amplitudes in all 3 animals implanted after the 5th month of life. Details in Kral et al. [2001]; for comparable human data see Lee et al. [2001].

Ponton et al. [1999, 2000a, b] and Ponton and Eggermont [review 2001, this vol.] have shown that there is a sensitive period in the development of the human auditory evoked potentials, ending around the age of 12 years. The fastest synaptic pruning in the auditory cortex is found between the 5th and 12th years [Huttenlocher and Dabholkar, 1997].

Sensitive periods were first known in the development of the visual system. Repair mechanisms after congenital binocular deprivation have a longer sensitive period than after monocular deprivation [cat 6–8 months, Cynader and Mitchell, 1980; Fregnac and Imbert, 1984]; after prolonged blindness the subsequent deficits in visual acuity and sensitivity are not fully reversible despite long-term visual experience [human data: van Senden, 1932]. In humans, the duration of the sensitive period for visual acuity has been assessed as 7–8 years [Daw, 1995]. These data, taken together, show similarities in the duration of the sensitive period in auditory and visual systems.

Mechanisms of Developmental Cortical Plasticity

Changes in innervation density of afferents from the medial geniculate body, changes in ramification of thalamocortical afferents or changes in callosal or other corticocortical projections may account for the reorganizations

described after chronic electrostimulation in congenitally deaf cats. Molecular mechanisms of these processes have not yet been clarified. The following section reviews possible mechanisms and the supporting literature.

Generally, it is assumed that mechanisms of synaptic plasticity, in particular long-term potentiation (LTP) [Bliss and Lomo, 1973] and long-term depression (LTD) [Ito, 1986], are responsible both for perceptual learning and reorganizations like those described in the present review. LTP at thalamocortical synapses (layers II/III and IV) can be elicited more easily in young animals [Crair and Malenka, 1995; Sermasi et al., 1999]. LTD in the visual cortex can also be elicited more easily in young animals, and the period in which LTD can be elicited is longer than the corresponding period for LTP [Rittenhouse et al., 1999]. The effects of LTP and LTD at thalamocortical synapses explain the development of amblyopia in monocularly deprived cats [Kirkwood et al., 1996].

The different susceptibility to LTP and LTD induction in the cortex is based on changes of glutamate receptors and their composition during development. In layer IV of the visual cortex, NMDA receptors present at birth are replaced by AMPA receptors later in the development [review in Kaczmarek et al., 1997]. NMDA receptors in other cortical layers themselves also undergo molecular changes during development [Hickmott and Constantine-Paton, 1997; Quinlan et al., 1999a, b; Tang et al., 1999]. A rearrangement of their subunits leads to changes in gating characteristics with the consequence of less calcium entering the neuron after agonist binding, which explains the lower plasticity. Changes in NMDA subunits similar to those in the visual cortex have been described in the cochlear nucleus [Förster and Illing, 1998] and can participate in synapse stabilization and elimination regulated by activity [Hickmott and Constantine-Paton, 1997; Segal et al., 2000; Colonnese and Constantine-Paton, 2001]. Interestingly, the change in the composition of NMDA receptors in the visual cortex is initiated by first light exposure and is delayed in dark-reared animals [Quinlan et al., 1999a, b]. Dark rearing can therefore participate in the prolongation of sensitive periods in complete deprivation [Cynader and Mitchell, 1980]. However, interspecies differences have to be considered: most in vitro experiments are undertaken in rodents, yet neurophysiological data are mostly based on cats and monkeys. Rodents differ in the development of the visual cortex [review in Katz, 1999]. Furthermore, the sensitive periods are not restricted to the time of eye-opening in cats, but can last for several months longer (see above). Consequently, additional factors have to be considered.

Inhibition seems to be related to sensitive periods in sensory development: the proportion of GABAergic cells increases around the end of the sensitive period in the visual cortex [Gao et al., 1999; Feldman, 2000]. In auditory cortex, the time course of GABAergic cell counts is similar to that in the visual cortex [Gao et al., 1999]. Inhibition has been suggested as one of the reasons for termination of the sensitive period [Fagiolini and Hensch, 2000]. Sensitive periods could be extended with complete deprivation by decreasing inhibition; even partial sensory loss down-regulates inhibition in the auditory cortex [Rajan, 1998; compare Fuchs and Salazar, 1998]. In neonatal rats, the function of inhibition differs from that in adults in a more dramatic way: in neonatal cortical layer I GABAergic synapses have excitatory effects [Dammerman et al., 2000]. In conclusion, numerous changes in inhibitory function take place during development that can participate in the existence and termination of a sensitive period.

Many findings demonstrate that synaptic plasticity is modulated over a substantial range, even in adults. In the auditory system, research has concentrated on cholinergic modulation [Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998; compare Kirkwood, 2000]. The cholinergic system seems to be one of the factors needed for synaptic plasticity in adults. There have been suggestions that the cholinergic system can also change the mode of information transfer from thalamocortical to corticocortical in the auditory cortex [Hsieh et al., 2000]. The cholinergic system can be expected to participate during sensitive periods [Aramakis et al., 2000]. Cholinergic influence is indeed increased during sensitive periods in the visual cortex and the increase is paralleled in the auditory cortex over the same time scale [Robertson, 1987; Robertson et al., 1991].

Nerve growth factor and brain-derived neurotrophic factor are also of crucial importance for cortical development. These factors influence the duration of sensitive periods in cats and rats [Galuske et al., 1999; Pizzorusso et al., 1999; Sermasi et al., 1999]. They participate in stimulation-dependent postnatal development, as their production is dependent on activity, and so are their effects on synaptic plasticity and dendritic growth [Boulanger and Poo, 1999; Caleo et al., 1999]. Brain-derived neurotrophic factor is down-regulated after eye-opening in rats and this down-regulation is postponed in dark-reared animals [Capsoni et al., 1999].

Conclusions

The central auditory system in congenital deprivation either cannot mature normally or degenerates because of the missing auditory experience. In congenital deafness, the excitability of the primary auditory cortex is decreased in the infragranular (output) layers. Indications of functional corticocortical and corticothalamic loops, i.e. long-latency activity in the primary auditory cortex and synaptic activity in infragranular layers, are missing. When auditory deprivation is ended early by electrical stimulation of the auditory nerve, e.g. by cochlear implants, the deficits can be overcome. These data stress the need for a neonatal auditory screening program and an early rehabilitation of children with hearing loss.

The mode of processing activity in the auditory cortex changes during early postnatal development. A large spectrum of finely regulated molecular mechanisms participates in this change. Many of them are known for the visual cortex, but their coordinated action is still not understood. In the auditory cortex they still need to be identified. Knowledge of the molecular mechanisms of postnatal auditory plasticity could open new therapeutic possibilities in congenital deafness and other central auditory deficits.

Acknowledgments

We are grateful to Dr. Jean Smolders for many critical discussions and comments on previous versions of the manuscript. The authors thank Karl-Friedrich Winter and Thomas Wulf for excellent custom-made technical equipment, e.g. the signal processors, and Natalie Krimmel for technical assistance. The animals were bred by Dr. Martin Kock and taken care of by Markus Behrendt, Sharon Büttner, Dana Sablakan, and Manos Pramateftakis. Supported by DFG (SFB 269).

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