Reference: Kral A, Hartmann R, Klinke R (2006): Recruitment of the auditory cortex in congenitally deaf cats. In: Lomber SG, Eggermont JJ (eds): Reprogramming the Cerebral Cortex. Oxford University Press, 191-210.

Chapter 10

Recruitment of the auditory cortex in congenitally deaf cats

Andrej Kral, Rainer Hartmann and Rainer Klinke

Developmental plasticity in sensory systems

As preceding papers have shown, plastic reorganization of neural networks is controlled by neuronal activity. It is initiated by synaptic changes based on long-term potentiation and long-term depression of synaptic efficacies, with the ultimate consequence of reshaping the neuronal network by axonal and dendritic reorganization. The capacity for plastic reorganizations can be influenced by numerous factors. Not only can neuromodulatory substances like norepinephrine or acetylcholine affect neuronal activity and plasticiy (Bakin and Weinberger 1996; Manunta and Edeline 1999). In addition, plastic changes play a more important role in the neocortex than in subcortical structures (Kaas *et al.* 1999). Furthermore, the potency for plastic changes in the auditory system is age-dependent, the earlier the higher (Kennard 1938; Harrison *et al.* 1991; Brainard and Knudsen 1998; Kapfer *et al.* 2002; Zhang *et al.* 2002). Neurotrophic factors are considered as the key elements in this process (Boulanger and Poo 1999). Also vice versa: activity can regulate the amount of neurotrophic substances produced by neurons and the number of receptors for neurotrophins (Zafra *et al.* 1992; Gall 1993; Meyer-Franke *et al.* 1998). They are in turn an essential trophic substance e.g. for denritic growth (McAllister *et al.* 1996).

Where does neural plasticity lead to under complete and long-term absence of any driven activity within the neural tissue? Do the same mechanisms that enable the nervous tissue to adapt to the needs of the environment deleteriously affect the neuronal networks if these remain inactive? We consider this question here using the central auditory system as a model.

Postnatal development of the afferent auditory system continues until adulthood both in humans (Conel 1939–1967) and cats (Eggermont 1996). That means that the development of the auditory system takes place also when the auditory system already performs discrimination and classification tasks important for the organism. Postnatal development is therefore supposed to depend on experience (Changeux and Danchin 1976; Eggermont, 1985; Wallhäuser and Scheich 1987; Kral *et al.* 2001; Chang and Merzenich 2003). At an early postnatal age, the neocortex develops very many synaptic contacts that are not maintained on a long-term basis. Activity helps to stabilize the synapses that are activated by the respective sensory input. Inactive synapses are useless in the given environment: the organism does not profit from their existence, and, as only activated synapses can learn, they also cannot adapt to new functions. Consequently, they are eliminated during postnatal development. Reductions in numbers of dendritic spines and synapses (*synaptic pruning*) have indeed been reported during postnatal development (Conel 1939–1967; Huttenlocher and Dabholkar 1997), the underlying molecular mechanisms are, however, not exactly known (compare Hickmott and Constantine-Paton 1997; Segal *et al.* 2000). This ability of young sensory systems to adapt to their inputs represents a prominent type of neural plasticity (*developmental plasticity*). A sensory system that developed without any sensory input will be referred to as a *naive* sensory system in the subsequent text.

The cochlea of congenitally deaf cats provides no input to the central nervous system

Experience, here understood as sensory input, is thus important for the appropriate development of sensory systems. The effect of auditory deprivation on the central auditory system has been studied with different animal models and methods. The present chapter investigates the changes in the auditory system of an animal model known as the congenitally deaf white cat (Mair 1973; Heid *et al.* 1998). The organ of Corti in these cats degenerates within the first two weeks of life, at a time when in normal kittens the cochlea is not yet functional. This degeneration leads to a cochlea completely devoid of any hair cells, yet with intact bony structures and preserved neuronal elements (Scheibe-type of dysplasia). Consequently, congenitally deaf cats are completely deaf. A longitudinal screening of auditory-evoked brainstem responses performed during the first 30 days after birth (Heid *et al.* 1998) revealed that no brainstem-evoked activity can be recorded in these animals, so that hearing experience can be safely excluded. Congenitally deaf cats also do not show any behavioral reactions to auditory stimuli. Thus, these animals have no hearing experience at all and represent a good model for studying developmental plasticity in a perceptually naive auditory system (Heid *et al.* 1998). In addition, plasticity of a naive auditory system can be studied with this model.

An important advantage of this deprivation model is the good preservation of the primary afferents of the auditory nerve (Heid *et al.* 1998). Ultimatitely, the primary afferents do degenerate, but the degeneration is very slow, comparable to human prelingual deafness (Felix and Hoffmann 1985; Vasama and Linthicum 2000). In the basal halfturn of the cochlea the spiral ganglion cells do not show a statistically significant cell loss during the first two years of life (Heid *et al.* 1998). In contrast, in pharmacologically deafened animals, both in guinea pigs as well as cats, the degeneration of spiral ganglion cells is rapid (Dodson 1997; Leake *et al.* 1999). The amount and pattern of activity evoked by electrical stimulation of the cochlea is influenced by the number of preserved spiral ganglion cells. This holds for pharmacologically deafened animals (Schwartz *et al.* 1993; Araki *et al.* 1997) as well as for congenitally deaf cats (CDCs). However, the proportion of surviving cells is larger in CDCs. Thus again, the congenitally deaf cat appears to be the adequate model.

Other models of auditory deprivation will not be directly discussed in this chapter, as they mainly concentrated on subcortical effects of auditory deprivation. The interested reader is referred to other recent reviews (Shepherd and Hardie 2001; Kral *et al.* 2001, Hartmann and Kral 2004).

Central auditory pathways in congenitally deaf cats are present

Congenitally deaf cats show several dystrophic changes in the central auditory system. Neurons in the brainstem show significant reductions of their somatic area in CDCs (Saada *et al.* 1996; Heid 1998; Redd *et al.* 2000). These effects are prominent in the superior olive and the cochlear nucleus (Heid 1998). However, neuronal numbers were not reported reduced in cochlear nucleus in this strain, similarly as in pharmacologically deafened cats (Leake *et al.* 1999). Electronmicroscopic analysis of synapses in the cochlear nucleus of CDCs demonstrated dystrophic and also hypertrophic, possibly compensatory changes (Larsen and Kirchhoff 1992; Ryugo *et al.* 1997; Ryugo *et al.* 1998). Reduction in the number of terminal ramifications, in the density of synaptic vesicles but also an increase in the size of the synaptic area and in pre- and postsynaptic densities were identified in CDCs.

However, the basic connectivity in the afferent auditory system of CDCs is comparable to that in hearing cats (Heid *et al.* 1997), including a nucleotopy. The afferent auditory pathway is

unchanged by auditory deprivation at least in gross measures of interconnections. Also the cochleotopic organization in the primary auditory cortex of these cats is rudimentarily present, as revealed by electrical stimulation through a multi-channel cochlear implant (Hartmann *et al.* 1997). This finding is very interesting, as experience can affect the tonotopic/cochleotopic organization of the auditory cortex. Long-term exposure to a constant pure tone during early development expands the representation of this tone at the auditory cortex (Stanton and Harrison 1996). It has additionally been shown that the tonotopic organization of the auditory cortex can be disrupted by unpatterned auditory stimulation within a critical (early) developmental period (Zhang *et al.* 2002). These data imply two different processes leading to the cochleotopic organization in the auditory cortex. The first one is most probably genetically determined and shows up also in congenitally deaf animals. The second process is epigenetical, based on maturational plasticity: it fine-tunes the genetically determined cochleotopic gradient by the biological importance of perceived stimuli. This latter process is more effective in an early developmental period.

In summary, the central auditory system of congenitally deaf cats appears to be developed in its basic properties. On the other hand, dystrophic changes were demonstrated in these animals.

Deprivation effects in the primary auditory cortex

To investigate the functional properties of the auditory cortex in adult congenitally deaf cats, an auditory input has to be provided to these animals. The only possibility to activate their auditory system is electrical stimulation of the primary afferents. To allow a comparison of the response properties obtained in CDCs with the ones from normally developed auditory systems, hearing cats have to be used as controls. To provide the same stimulation conditions, electrical stimulation of the hair cells in hearing controls (cochlear 'electrophonic response') (Kiang and Moxon 1972) has to be prevented. This is achieved by an acute pharmacological destruction of hair cells by intracochlear application of neomycin at the beginning of the experiment.

To determine the lowest cortical thresholds in lightly anaesthetized animals (Kral *et al.* 1999) stimulated through a cochlear implant, local field potentials were recorded using Ag/AgCl electrodes (diameter 1 mm) at a regular grid of 3×3 positions within the primary auditory cortex for pulsatile electrical stimulation of the cochlea. In hearing controls as well as in CDCs the amplitude-intensity functions (Figure 10.1) had a saturating shape and a rather small dynamic range of 4–6 dB (Hartmann *et al.* 1997). Lowest thresholds of cortical field potentials (i.e. thresholds of Pa waves, compare. Figure 10.1) were reduced in CDCs on average by 5.2 dB (Kral *et al.* 2005). However, no difference was found in electrically evoked brainstem response thresholds. Thus, the structures providing input to the auditory cortex, mainly the generators of the Pa wave (layer III), seem to become more sensitive to thalamic input by deprivation.

In a second step, the auditory cortex was mapped using local field potentials (LFPs) recorded at the cortical surface through a glass microelectrode. The stimulation was set 10 dB above the lowest cortical threshold, where the amplitude-intensity functions were safely in saturation (arrows in Figure 10.1). This guaranteed that no large error in the functional maps would result even if lowest cortical thresholds would over- or underestimate the cortical thresholds. Within the maps a region of interest (ROI) was defined (area $= 1\ mm^2$) comprising the positions with largest LFPs. Further analyses and recordings were performed within the ROI.

Neural activity within ROI was investigated by current source density analyses (CSD) of local field potentials. The CSD method eliminates far-field influences from the LFPs and essentially computes the extracellular components of local transmembrane currents flowing near the electrode tip (Mitzdorf 1985). These CSDs mainly originate from large cells with vertically oriented dendrites. CSDs estimate synaptic activity; action potentials contribute to the CSD only to a minor extent.

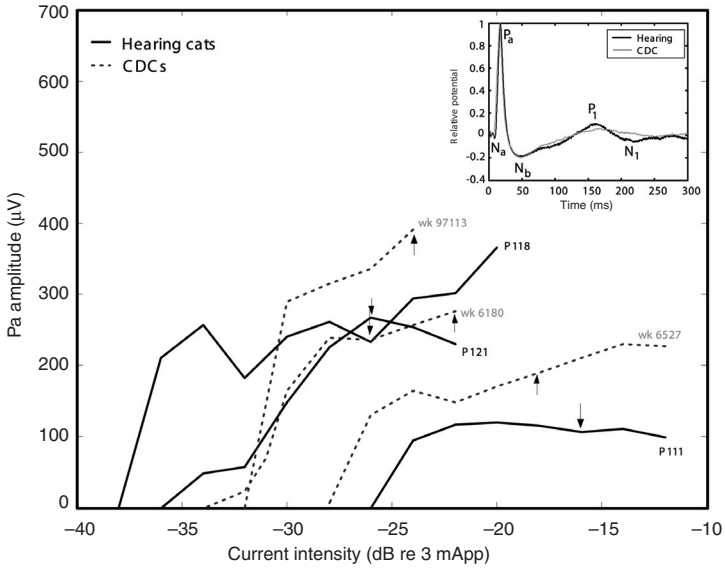

Figure 10.1 Amplitude-intensity functions of P_a-waves of cortical local field potentials in response to electrical stimulation through a cochlear implant (compare also Hartmann *et al*. 1997). Amplitude intensity functions have a dynamic range of < 6 dB and have a saturating shape in the majority of recording positions. To prevent electrophony in hearing controls, the hair cells were destroyed at the beginning of experiment by introcochlear infusion of neomycin. The arrow marks the intensity of 10 dB above lowest cortical thresholds, where cortical mapping was performed. Hearing controls: P111, P118, P121; congenitally deaf cats: wk 97113, wk 6180, wk 6527. Inset: shape of a mean local field potentials from the most-activated cortical area in an adult CDCs and hearing control.

First, local field potentials (LFPs) were recorded at different cortical depths during penetration of a microelectrode through all layers of the auditory cortex (Kral *et al*. 2000). From these data, one-dimensional current source densities in the direction of the penetration (i.e. perpendicular to the cortical surface) were computed. Histological reconstruction of the electrode penetrations allowed the assignment of cortical layers to recording depths.

The method allowed reconstruction of the spread of excitation within the primary auditory cortex. In *hearing cat* activation starts more or less simultaneously in layers VI, V, IV, and III. Activity then spreads into layers III/II, resulting in large sinks in these layers, mainly in layer III. Next, activity shows up in infragranular layers V and VI. In hearing cats the patterns of cortical activation spread over the whole investigated temporal windows of 50 ms post-stimulus up to 300 ms (Figure 10.2, Klinke *et al*. 1999). The pattern allows interpretation of the morphology of surface-recorded LFPs (compare Kral *et al*. 2000):

- The cortical input into layer IV generates the Na wave on the cortical surface.
- The surface-positive large P_a wave is correlated with a large sink in layer III. This sink might be caused by the activation of the cartridge synapses of stellate cells on the dendrites of pyramidal cells in layer III.
- The early sinks in layer III/IV were followed by a source in these layers, with a sink in layer II/upper layer III. This could either represent an excitatory current in layer II or an inhibitory current in layer III that limits the duration of excitation in layers III/IV (*postexcitatory inhibition*). As few multi-unit responses were observed after the initial onset response (Klinke *et al*. 1999, Kral *et al*. 2001) in these layers in field A1, the latter explanation becomes more

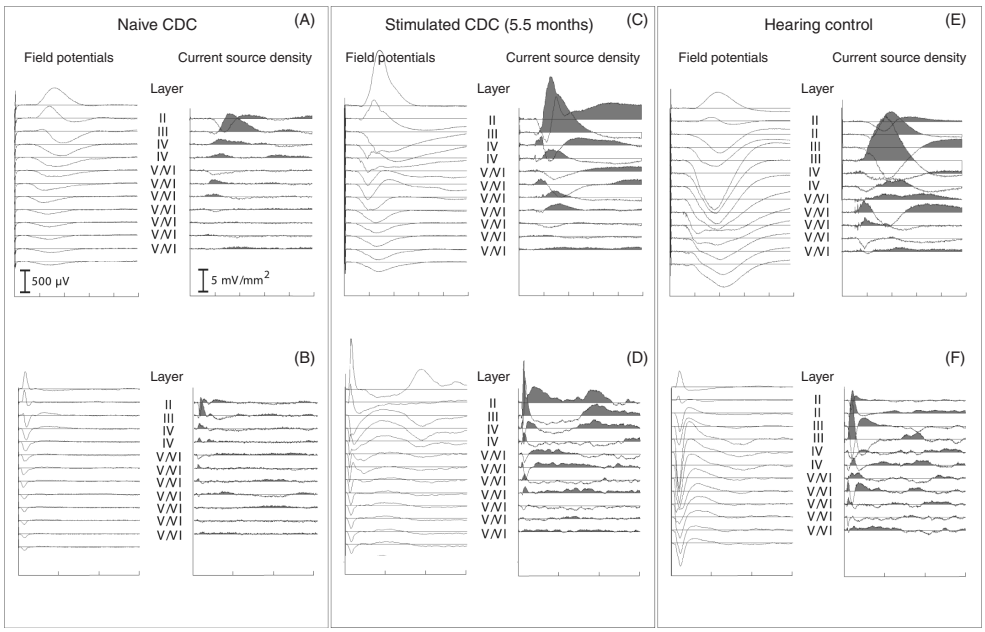

Figure 10.2 Local field potentials and the corresponding current source densities computed from the auditory cortex of a naive cat (A,B), chronically stimulated cat (C,D) and a hearing control (E,F). Sinks, representing the inward transmembrane currents, are shaded. Reprinted, with permission, from Klinke *et al*. 1999.

probable. This cortical inhibition in layers III/IV possibly generates the long-lasting wave N_b on the surface of the cortex. The inhibition generates a passive backward current in layer II, so that the dendrites of the cells have to extend up to these layers. Most probably the cells generating the P_a wave are inhibited as a consequence of a feed-forward inhibition.

In contrast, the congenitally deaf cats showed less synaptic activity within the primary auditory cortex (Figure 10.2). The peak amplitude of the sinks computed over 50 ms post stimulus was significantly smaller by ~30–40 per cent (Figure 10.3). These deficits appear during the phase of auditory maturation (Kral *et al.* 2005). However, older animals showed further decrements in the mean sink amplitude, showing that a process of cortical degeneration proceeds into adult age. The decrease of sink amplitudes was most prominent at latencies longer than 30 ms and in infragranular layers.

Also the pattern of cortical activity differed from hearing controls: in CDCs the shortest latencies of transmembrane currents (CSDs) were significantly increased, the earliest sink in supragranular layers II/III was either missing or substantially delayed, and the activity in infragranular layers V/VI was reduced (Kral *et al.* 2000). These data allow the following interpretations: the increase in latency of sinks in supragranular layers relative to the cortical input to layer IV indicates a desynchronization of different synaptic inputs on large, vertically oriented cortical cells (most probably pyramidal cells). This can essentially affect columnar processing (Larkum *et al.* 1999; compare Cruikshank *et al.* 2002): synchronous activation of layer V pyramidal cells can bring the cell into a bursting mode of spiking, and bursts and ongoing activity are believed to be important for cortical processing. Preventing the bursting mode by a delay of synaptic activity in supragranular layers may thus impair further processing in the cortical column and prevent the generation of normal columnar output to other cortical areas and the thalamus.

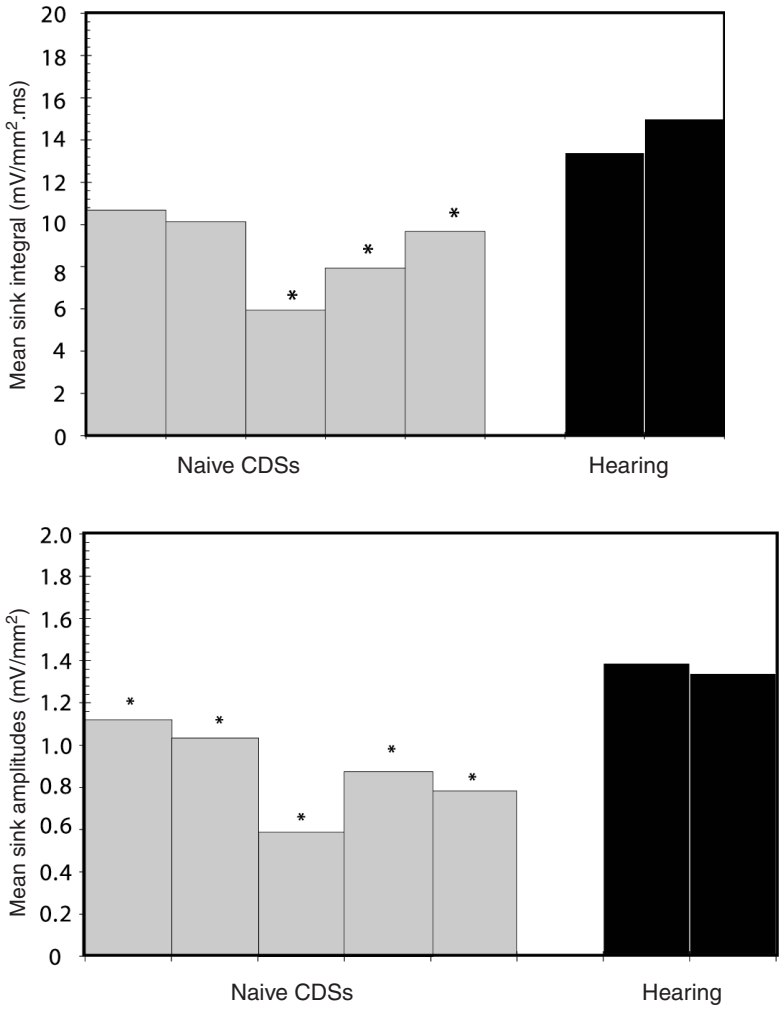

Figure 10.3 Comparison of mean sink integrals and mean amplitudes of sinks in naive cats and hearing controls. Each bar represents one animal. Significant difference to pooled hearing cats is indicated by an asterisk (Wilcoxon-Mann-Whitney test at $\alpha = 5$ per cent).

To clarify the reasons for the decrease in synaptic activity in CDCs, local field potentials were analyzed by independent component analysis (Hubka, *et al.* 2004). This analysis reveals the statistically independent components contributing to the field potentials. To investigate the generators of the independent components, these were further analyzed using the CSD method. With this method a more uniform activation of the cortical layers at neighboring recording positions was revealed in congenitally deaf cats. One possible interpretation is that functional uniformity, irrespective of recording position, is a sign of immature cortical processing. Additionally, the computed independent components were significantly broader in CDCs. Desynchronization of synaptic activity at individual synaptic 'patches' generating one independent component would explain such 'broadening' of synaptic activation.

In summary, local field potentials and their mathematical analysis demonstrate that the evoked neural activity in the primary auditory cortex is reduced in CDCs, despite a hypersensitivity at

threshold intensities. The pattern of cortical activation is altered and ceases already after 30 ms post stimulus, compared to activity up to 300 ms in hearing controls. Desynchronization of cortical activity results in insufficient activation of infragranular layers. Also the activation of neighboring cortical columns is more uniform in CDCs. All these data most likely reflect functional immaturity of the auditory system in CDCs.

The data thus far were supported by multi-unit activity recorded in CDCs (Hartmann *et al.* 1997, Kral *et al.* 2001). Cortical multi-unit activity showed a relatively uniform pattern. Both for stimulation with pulses and for stimulation with short sinusoidal stimuli the amplitude–intensity functions were uniformly of saturating shape. The thresholds were a simple function of the current delivered into the cochlea. The longer the duration of the electrical stimulus the lower was the threshold. In 99 per cent of the recorded units the poststimulus time histogram showed a simple onset pattern with small variation of onset latency. Following months of hearing experience this uniformity disappeared (see section 'Hearing experience through cochlear implants is possible').

The above findings on CDCs provide first evidence of a decrease in cortical synaptic activity as a consequence of congenital auditory deprivation. These findings are supported by morphological data from other sensory systems: the number of synapses decreased in visual cortex after visual deprivation, both in cats and monkeys (Cragg 1975a,b; Winfield 1981; O'Kusky and Colonnier 1982; O'Kusky 1985). Our own data also indicate a decrease in number of dendrites and their ramifications in the primary auditory cortex of congenitally deaf cats (Figure 10.4). Both the reductions of synaptic currents as well as dendritic ramifications are most probably the consequence of the normal postnatal synaptogenesis. In absence of auditory experience the cortex seems to functionally eliminate more synapses than in hearing controls.

Can an auditory input after a period of congenital deafness allow such plastic reorganization that the auditory system gains sufficient competence to process auditory information?

Hearing experience through cochlear implants is possible

To investigate whether the described deficits are reversible in congenital deafness it is necessary to provide deaf animals with auditory experience. For this reason the CDCs were provided with a cochlear implant. Single-channel monopolar stimulation was applied using a portable signal processor Klinke *et al.* 1999, 2001 Kral *et al.* 2001, 2002). The stimulation strategy used was similar to the one used in human Vienna-type speech processors (a single-channel compressed analogue strategy). The device provided the animals with temporal information on the sounds, however, place coding was absent. The animals continuously 'heard' all ambient and self-produced sounds in the range of 100 Hz–8 kHz and with intensities above 65 dB SPL (24 hrs a day 7 days a week). To encourage an active use of hearing, the animals were additionally conditioned to acoustic stimuli. They learned to pick up a reward whenever they heard a tone of a given frequency. A success rate of $>$80 per cent was reached within 2–4 weeks (Klinke *et al.* 1999). The animals also learned to search for sources of acoustic stimuli, appropriately react to calls and showed a biologically relevant acoustic behavior.

Post-mortem analysis of the implanted cochleae showed that in all but one animal the implant did not rupture the basilar membrane. It was embedded in connective tissue filling out the scala tympani. Histological analysis of the brainstems of chronically stimulated animals showed that the somatic area of cochlear nucleus neurons significantly increased in comparison to naive CDCs and approached the somatic areas of hearing controls (Heid *et al.* 2000). Eight weeks of hearing experience were necessary to reach the level of statistical significance. A similar effect was observed in the superior olivary complex. However, here a significant somatic area expansion was found after four weeks of hearing experience.

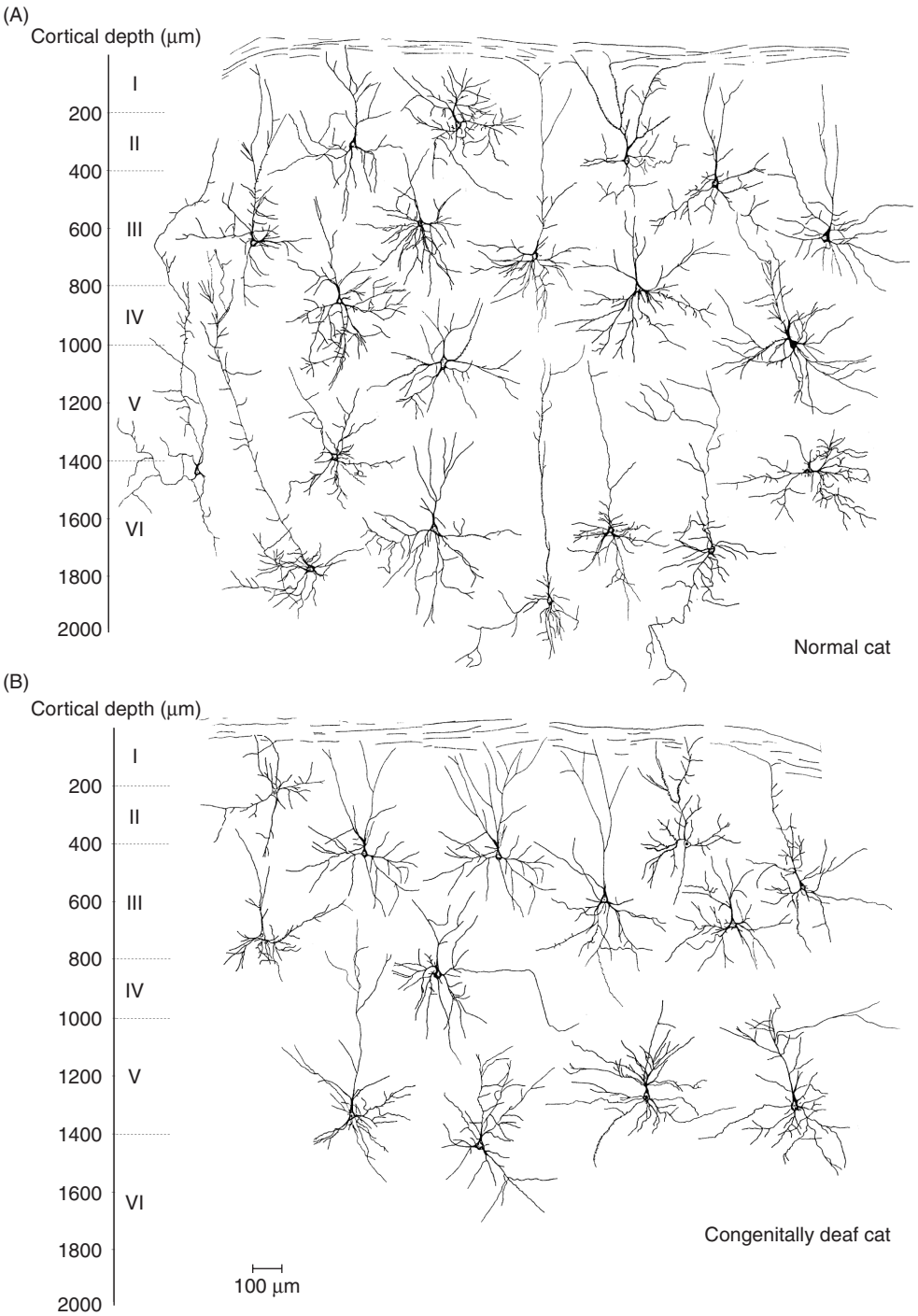

Figure 10.4 A representative collection of camera lucida drawings of neuronal dendritic trees from field A1 of a normal hearing cat (top) and a congenitally deaf cat (bottom). Picture by N. Wurth and S. Heid (compare Wurth 1999).

After a long period of chronic electrostimulation, the auditory cortex of the animals was investigated in neurophysiological experiments. The experimental paradigm was similar to the one described in the section entitled 'deprivation effects in the primary auditory cortex'. The lowest cortical threshold did not significantly change in comparison to naive CDCs. However, the amplitude of local field potentials increased (Klinke *et al.* 1999). Long-latency P_1 waves were also better discernible in chronically stimulated animals than in naive CDCs (Figure 10.5).

For further comparisons, a 'cortical activated area' was defined as the area comprising LFPs larger than 300 μV. There was an expansion of the cortical activated area in course of the chronic electrostimulation (Figure 10.6) (Klinke *et al.* 1999, Kral *et al.* 2002). The effect of the expansion was very prominent, reaching a factor of five when compared to deaf animals. This massive effect was considered as a consequence of the artificial single-channel stimulation, providing biologically relevant auditory input through only one, although large cochlear section (monopolar configuration) (compare Kral *et al*. 1998). Consequently, the representation of this segment expanded in the auditory cortex (compare Robertson and Irvine 1989; Recanzone *et al.* 1993; Kilgard and Merzenich 1998; Pantev and Lutkenhoner 2000). This effect was considered as a plastic reorganization of the auditory system by the artificial single-channel stimulation. The expansion was slow, requiring months of experience to develop. Consequently, this effect is most probably connected to structural changes, either at the cortex or also subcortically. Similar findings, although of a lesser extent, were present also in the inferior colliculus of chronically stimulated neonatally deafened cats (Snyder *et al.* 1990). Whether this subcortical reorganization was cortically induced has not been verified yet, but appears probable (compare Ma and Suga 2003; Suga *et al.* 2000; Ergenzinger *et al.* 1998).

There was also a change in the shape of LFPs due to the chronic electrostimulation. The P_a wave had shorter duration, there was a decrease in latency of the P_b wave and the long-latency responses (P_1 waves) increased in amplitude after hearing experience (Klinke *et al*. 1999, Kral *et al.* 2002).

Multi-unit activity within the ROI revealed more complex response properties in chronically stimulated animals when compared to naive CDCs. Post-stimulus time histograms in response to short-duration sinusoidal or pulsatile stimuli showed response types rarely or never observed in naive CDCs. Consequently, more multi-unit classes could be differentiated in chronically

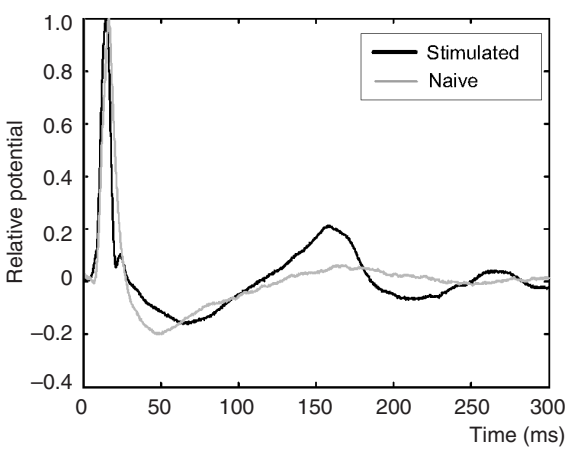

Figure 10.5 Comparison of normalized mean local field potentials from the most activated cortical area within field A1 between a naive and a chronically stimulated cat (Klinke *et al*. 1999; Kral *et al*. 2002).

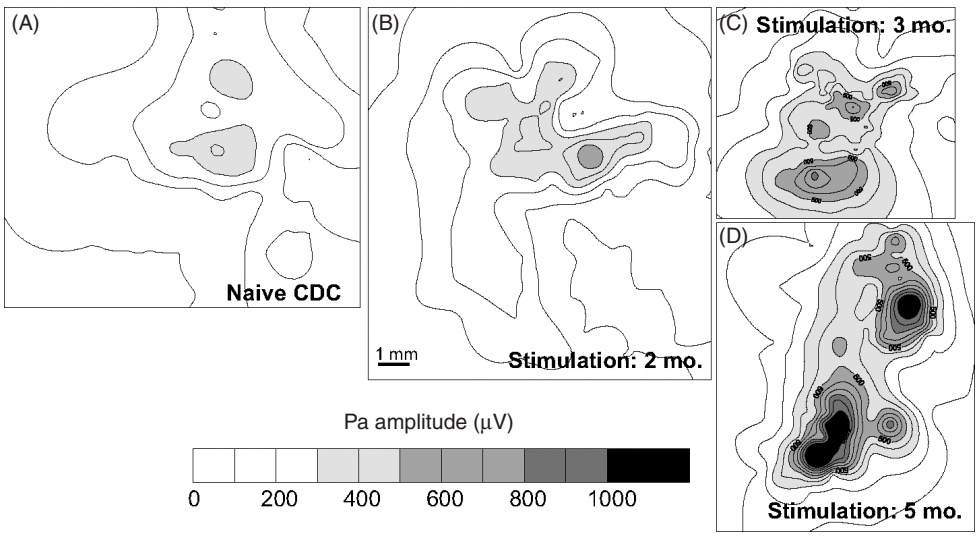

Figure 10.6 Cortical activation maps computed from Pa–waves of surface-recorded local field potentials in a naive cat (A) and three chronically electro-stimulated cats (B,C,D) implanted at the age of ~3 months. The cortical activated area significantly expands with stimulation duration (Kral *et al*. 2002).

stimulated animals than in deaf cats (Klinke *et al*. 1999). Additionally, the rate-intensity functions were more complex and differed in shape for different types of stimuli (Kral *et al*. 2001). A very prominent finding was the increase in the proportion of units demonstrating long-latency responses in post-stimulus time histograms (chronically stimulated: 43 per cent, naive: 1 per cent). These data provided evidence that the same stimulus can be responded to in different ways by different units, and that the same unit responded differently to different types of stimuli. This was more prominent in chronically stimulated animals than in naive cats. Consequently, auditory experience led to a diversification of the functional properties of the auditory cortex, in other words a functional maturation of the auditory cortex took place.

When synaptic activity was investigated in chronically stimulated animals, the CSD profiles appeared more similar to hearing cats than the CSDs of naive animals (Figure 10.2, Klinke *et al*. 1999). The mean amplitudes of CSDs, when analyzed over 50 ms post-stimulus, became significantly larger than in naive cats. In naive animals the cortical synaptic activity had already ceased after 30 ms. In comparison, the chronically stimulated animals showed long-term activity up to 300 ms post stimulus. This phenomenon indicated that the previously described deficits in the auditory cortex of naive animals became compensated for by the long-term auditory experience through cochlear implants. Largest increases in CSD amplitudes were found in supragranular layers (mainly layer III), where plasticity is known to be greatest.

Additionally, there was also an effect of chronic hearing experience on the activation pattern in the cortex (Figure 10.2, Klinke *et al*. 1999). The pattern of cortical activation became comparable to hearing animals. Not only was the delay in supragranular activation counterbalanced, but the infragranular also layers became activated. This normalization in the cortical activity indicates that the cortical column became functional after long-term electrostimulation. An activation of

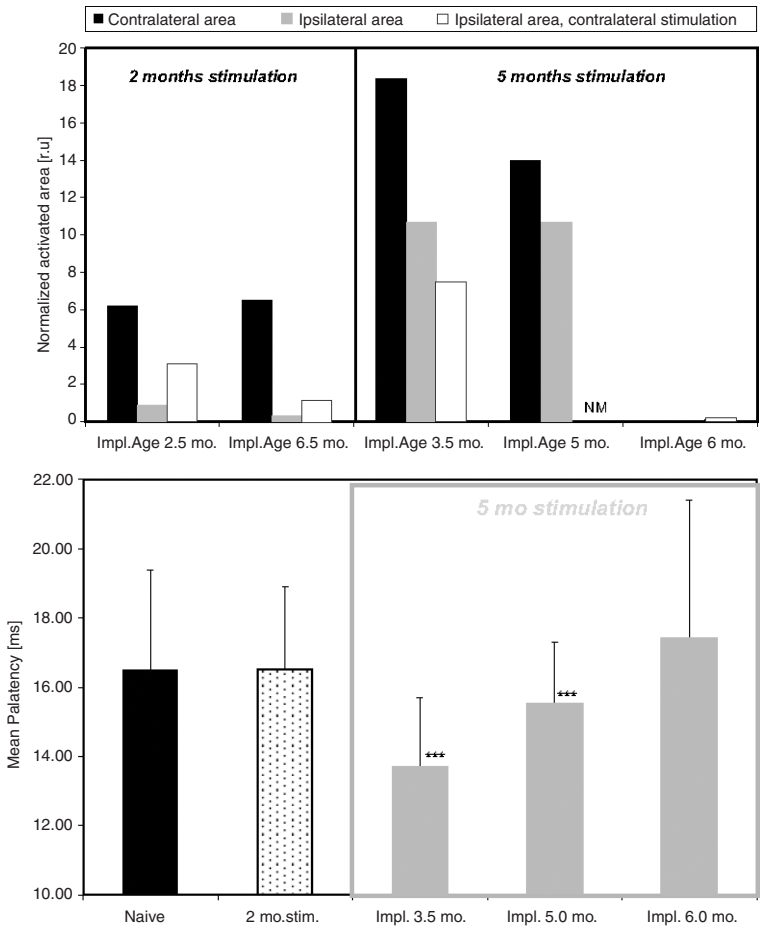

Figure 10.7 Effect of age at implantation on the cortical activated area and P_a latency. Left: Activated areas at the cortex ispilateral and contralateral to the chronically stimulated ear. Contralateral stimulation means that the ear that was not stimulated chronically was implanted in the final experiment and stimulation took place there (i.e. contralateral to the chronically stimulated ear). Nomenclature of the cortex is always relative to the chronically stimulated ear. Right: P_a latency as a function of implantation age. Naive animals and animals stimulated for two months were pooled, as no effect of implantation age was found in these animals. After five months of stimulation, there was a significant increase of P_a latency with implantation age. These data demonstrate the existence of a sensitive period in the auditory cortex of cats (Kral *et al*. 2001, 2002).

efferent (descending) structures of the primary auditory cortex like higher auditory cortex or thalamus appears possible after chronic electrostimulation.

Another interesting finding was the effect of age at implantation on these cortical changes. The later the implantation took place, the smaller were the expansions of the activated areas (Figure 10.7) (Kral *et al*. 2002). Thus in CDCs the plasticity of the auditory system decreased with increasing age within the first six months of life. Correspondingly, the P_a latencies significantly

decreased after five months of auditory experience. However, the decrease was significantly smaller with increasing implantation age, and at implantation age of six months P_a latencies remained the same as in naive animals (Figure 10.7). The shape of later responses after long-term chronic electrostimulation also demonstrated changes consistent with a sensitive period in the auditory system (Kral *et al.* 2002). Corresponding sensitive periods in the cortical plasticity are known also in humans (Sharma *et al.* 2002a,b,c; Ponton and Eggermont 2001; Ponton *et al.* 1999; compare Chapter 11 this volume).

Unfortunately it is unknown what takes place in the higher-order auditory cortex in these animals. There are, however, data on the auditory cortex of humans that became deaf and were provided with a cochlear implant (Naito *et al.* 1997; Giraud *et al.* 2001a,b,c; Lee *et al.* 2001). These studies presented evidence that the primary auditory cortex can be activated by a cochlear implant even after long periods of deafness. On the other hand the secondary auditory cortex became activated only rudimentarily and, in late-implanted patients, remained only rudimentarily activated even after several months of hearing experience through the implant (Naito *et al.* 1997).

The P_1-waves of cortical evoked potentials are most probably generated mainly in higher-order auditory cortex. Consequently, human data demonstrating maturation of P_1 waves in early implanted cochlear implant users[1] (Ponton *et al.* 1996a, b; Ponton and Eggermont 2001) most probably reflect the maturation of higher-order cortex.

No cross-modal reorganization of the primary auditory cortex

The potential cross-modal recruitment of the deprived primary auditory cortex is unknown. One popular hypothesis is a cross-modal reorganization gradually taking place in postnatal life. Nonetheless, the decreased cortical thresholds to peripheral auditory stimulation in the deprived primary auditory cortex (see above) point to another direction: if the primary auditory cortex received input activity from another sensory system, it would most probably de-couple from the auditory thalamus. That would in turn lead to an increase in neuronal threshold for auditory inputs, in contrast to our findings. This contradiction already indicates that such a reorganization does not take place in the *primary* auditory cortex of CDCs.

Reports concerning a recruitment of field A1 by the visual system are controversial: multi-unit responses to visual stimulation were found neither in an unanesthetized congenitally deaf cat nor a hearing cat (Stewart and Starr 1970). Reports from the visual system support this hypothesis: even after enucleation the primary visual cortex does not show more than 16 per cent of units responsive to auditory stimulation (Yaka *et al.* 1999).

In contrast, Rebillard and colleagues report on the cross-modal reorganization of the primary auditory cortex in congenitally deaf cats. The authors described visually evoked local field potentials in A1 (Rebillard *et al.* 1977, 1980). Recordings were performed at the cortical surface with large (Ag/AgCl) electrodes, stimulation was with visual flashes. This method, however, is not focused on neural activity within A1 – large-scale electrodes also record also far fields from other cortical areas. Indeed, Hartmann and colleagues (1997), using the same technique, did not confirm Rebillard's conclusions. The study showed that visually evoked potentials can be recorded from many non-visual areas and decrease in amplitude with increasing distance from visual cortex.

In a follow-up study (Kral *et al.* 2003) recordings were performed using microelectrodes. Both field potentials and multi-units were recorded in A1 of adult cats. For stimulation, in addition to visual flashes phase-reversal gratings of different orientations and spatial frequencies were used.

1 The P1-waves in local field potentials may not correspond to P1-waves in human evoked potentials.

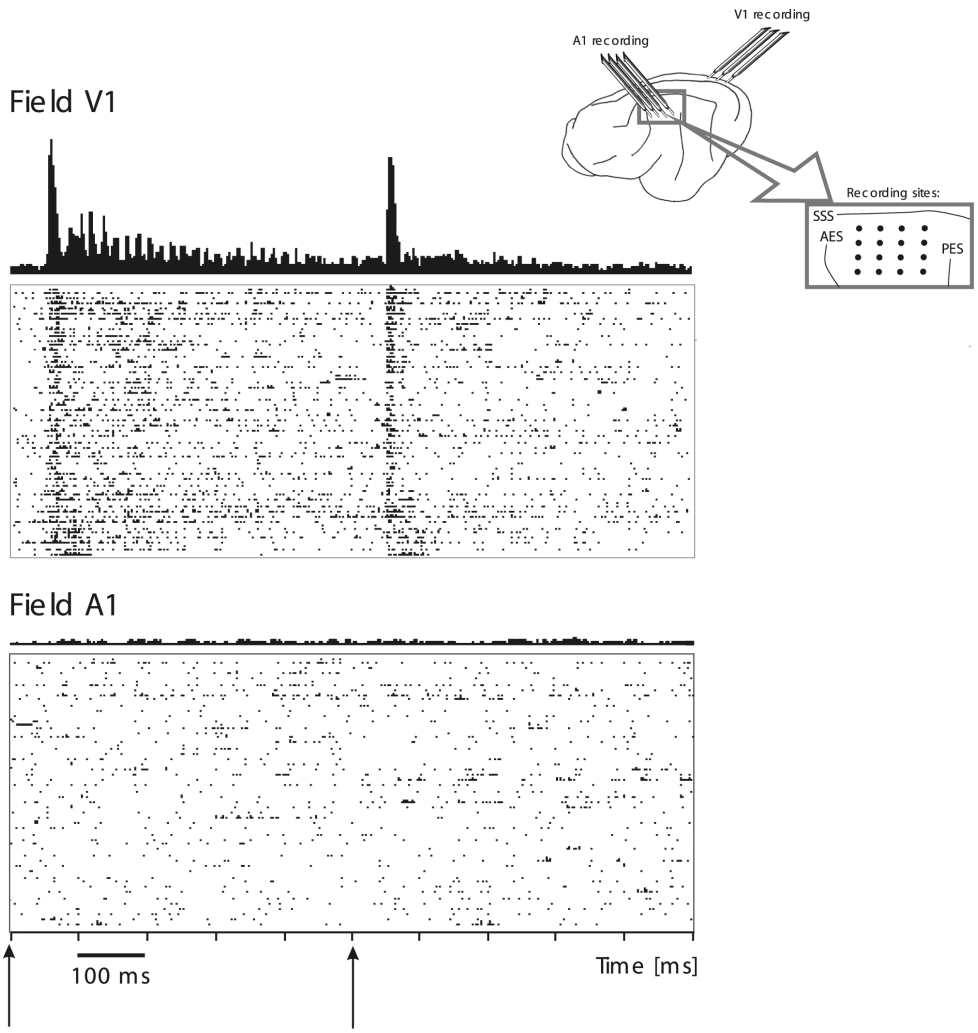

Figure 10.8 Response of simultaneously-recorded units in the area V1 and A1 in response to visual stimulation (phase-reversal gratings). On the top is the post-stimulus time histogram, on the bottom the corresponding dot-display of the responses. No response was found in area A1, whereas a strong on response with following γ-band activity was found in area V1, demonstrating an efficient visual stimulus. Inset: Recording positions of microelectrode arrays for simulteneous recordings in area A1 and V1 and the recording grid at the surface of A1. AES: anterior ectosylvian sulcus, PES: posterior ectosylvian sulcus, SSS: superior suprasylvian sulcus. Details in Kral *et al*. (2003).

Phase-reversal gratings activate both the motion-sensitive (dorsal) and pattern-sensitive (ventral) processing streams. They allowed additional testing of the responsiveness to visual motion in auditory cortex as previous reports indicated that visual motion might be analyzed in cross-modally reorganized auditory areas in congenitally deaf subjects (review in Bavelier and Neville 2002).

In these experiments visually evoked local field potentials were recorded in field A1 of both hearing and deaf cats, but more often in deaf cats (Kral *et al*. 2003). On the other hand, the amplitudes of the responses were small ($<$50 μV) and the latencies were not significantly different

from field potentials simultaneously recorded in the visual cortex. Current-source density analyses of these data did not reveal any generators of these potentials within the primary auditory cortex. When multi-unit responses were evaluated (Fig 10.8) , the proportion of units showing a possible modulation of the post-stimulus time histograms after visual stimulation was small (<1 per cent) and identical in hearing and deaf cats. Also no responses to somatosensory stimulation were found within the primary auditory cortex in these animals.

These data indicate that there are certain constraints in cross-modal reorganization after sensory deprivation: *primary* areas do not seem to be capable of massive cross-modal reorganization reported in secondary (higher-order) cortices. Possibly the abundant projections from the lemniscal thalamus limit the capacity for cortical cross-modal reorganization. Of course, the field A1 could have been recruited also by other, not-tested senses like gustatory or olfactory inputs. And the light anaesthesia necessary in these experiments could have been responsible for the absence of responses to visual stimuli, as anaesthesia suppresses polysynaptic neuronal pathways. On the other hand, with similar stimuli and same light anaesthesia multi-unit responses have been recorded in higher-order visual areas (19, 21) neighboring the auditory areas (area 21: Dreher *et al*. 1996; PMLS and PLLS: Blakemore and Zumbroich, 1987; review in Spear, 1991). Even a subthreshold activation should have been detected by the current-source density method.

The primary auditory cortex of CDCs thus most probably remains dormant in CDCs. Similarly, except for spontaneous activity, huge parts of the afferent auditory system remain inactive although morphologically present in naive animals. There are reasons to assume that primary and higher-order auditory cortex are different in their capacity for plastic reorganizations, as they do not share the same inputs. The main driving force in primary cortical areas is the afferent sensory pathway, whereas higher-order cortices do have mainly cortical and less-specific thalamic inputs. Some inputs to higher-order cortices originate in different sensory systems, so that these areas receive polysensory information even in undeprived subjects (for the auditory system compare Schroeder *et al*. 2001).

Primary auditory cortex has not been shown to be the target of projections from other modalities. The existence of projections from the primary auditory into the non-foveal representations of primary visual cortex, however, has been demonstrated in young kittens (Innocenti and Clarke 1984; Innocenti *et al*. 1988; Falchier *et al*. 2002). During early postnatal development these projections are reduced in number. It is not quite clear whether these projections are functional and what the function of these projections is. One interpretation is that they allow directing the visual attention to an auditory-salient stimulus. If there is a projection from primary auditory cortex to primary visual cortex, a reciprocal projection appears reasonable. However, a back-projection from the visual cortex to the auditory cortex would be of lesser benefit, as the response latencies in the primary visual cortex are in the range of 40–50 ms, compared to 8–12 ms in the auditory cortex. The activity coming from the primary visual cortex would then reach the primary auditory cortex too late for any attention effects. Rather it would most probably coincide with the phase of post-excitatory inhibition in the auditory cortex. Consistent with this finding no projections from visual to the auditory cortex could be identified so far.

Implications for research on auditory plasticity

The presented data demonstrate a remarkable plasticity of the auditory system during development. In absence of auditory inputs developmental processes lead to elimination of so many synapses in the auditory cortex that it loses the competence to process afferent activity.

However, the primary auditory cortex of congenitally deaf cats can be activated by stimulation of the auditory nerve, indicating that the cortical input is preserved even after long periods of

deafness. More pronounced deficits were found at longer latencies and in infragranular layers. The infragranular layers are upstream in the processing within the cortical column. CDCs are not capable to appropriately activate pyramidal cells in layers V/VI that are important for generating the output of a cortical column. Decrease in activity of infragranular layers and at longer latencies indicate that the upstream processing within the cortical column is compromised by congenital deafness. A second consequence is the compromised cortico-cortical and cortico-halamic processing. This would implicate a functional decoupling of the primary auditory cortex from the higher-order areas. This neuropathophysiology seems to represent the basis of perceptual deficits and ill-performance in prelingually deaf, late-implanted subjects (Busby *et al*. 1992, 1993; Fryauf-Bertschy *et al*. 1997; Busby and Clark 1999; Tyler *et al*. 2000) (see below). Congenital auditory deprivation also prevents or eliminates the normal functional diversity of neighboring cortical columns, so that the resulting activity is more uniform and unstructured.

Chronic electrostimulation demonstrated that the above processes are reversible, to a certain extent. Both the infragranular activity as well as the long-latency activity increase if auditory input is provided. Consequently, the deficits described above are indeed a consequence of auditory deprivation. They can be reversed, provided that auditory stimulation is resumed early enough. The auditory cortex can learn to process the inadequate electrical stimulus: with chronic electrostimulation the diversity of single- and multi-unit responses increases, showing long-latency responses, highly non-monotonic rate-intensity functions, expanded dynamic range and different types of post-stimulus time histograms. Units 'learn' to respond to different stimuli in different manners, and different units also responded to the same stimulus differently. Thus, the primary auditory cortex functionally matured under chronic electrostimulation. These maturational functions finally lead to an adequate acoustic behavior.

Several conclusions can be drawn from the above-mentioned studies on auditory plasticity:

1. The functional properties of an adult auditory cortex are both the consequence of genetically determined developmental sequences and experience-dependent shaping of the functional properties in postnatal life. Maturation depends on experience.
2. Naive (unexperienced) animals show deficits in their auditory cortex. These most probably lead to a decoupling of the primary and higher-order cortices.
3. Hearing experience after periods of congenital deafness allows a catch-up for functional development, provided the experience takes place relatively early in life. Late auditory experience induced less reorganization and functional adaptation than an earlier one. Consequently, the auditory system shows a sensitive period during development. These conclusions are supported by animal research, human psychophysics, evoked-potential studies on humans and functional imaging in humans (see Chapter 11).

Acknowledgment

The data for this chapter were obtained from a collaboration with Drs Silvia Heid and Jochen Tillein. Peter Hubka performed the independent component analysis of local field potentials. The excellent technical support of Natalie Krimmel and Harald Schalk is acknowledged. The project was supported by DFG (SFB 269).

References

Araki S, Kawano A, Seldon HL and Clark GM (1997). Intracochlear factors affect the auditory brainstem response to intracochlear electrical stimulation in the cat. *Cochlear Implant and Related Sciences Update*, **52**, 39–42.

Bakin JS and Weinberger NM (1996). Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proceedings of the National Acadamy of Science of the United States of America*, **93**, 11219–24.

Bavelier D and Neville HJ (2002). Cross-modal plasticity: where and how? *Nature Reviews Neuroscience*, **3**,443–52.

Blakemore C and Zumbroich TJ (1987). Stimulus selectivity and functional organization in the lateral suprasylvian visual cortex of the cat. *Journal of Physiology*, **389**, 569–603.

Boulanger L and Poo MM (1999). Presynaptic depolarization facilitates neurotrophin-induced synaptic potentiation. *Nature Neuroscience*, **2**, 346–51.

Brainard MS and Knudsen EI (1998). Sensitive periods for visual calibration of the auditory space map in the barn owl optic tectum. *Journal of Neuroscience*, **18**, 3929–42.

Busby PA and Clark GM (1999). Gap detection by early deafened cochlear-implant subjects. *Journal of the Acoustical Society of America*, **105**, 1841–52.

Busby PA, Tong YC and Clark GM (1992). Psychophysical studies using a multiple-electrode cochlear implant in patients who were deafened early in life. *Audiology*, **31**, 95–111.

Busby PA, Tong YC and Clark GM (1993). Electrode position, repetition rate, and speech perception by early- and late-deafened cochlear implant patients. *Journal of the Acoustical Society of America*, **93**, 1058–67.

Chang EF and Merzenich MM (2003). Environmental noise retards auditory cortical development. *Science* 300: 498–502.

Changeux JP and Danchin A (1976) Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. *Nature*, **264**, 705–12.

Conel JL (1939–1967). *The Postnatal Development of Human Cerebral Cortex. Vol. I–VIII*. Harvard University Press, Cambridge, MA.

Cragg BG (1975a). The development of synapses in kitten visual cortex during visual deprivation. *Experimental Neurology*, **46**, 445–51.

Cragg BG (1975b). The development of synapses in the visual system of the cat. *Journal of Comparative Neurology*, **160**, 147–66.

Cruikshank SJ, Rose HJ and Metherate R (2002). Auditory thalamocortical synaptic transmission *in vitro*. *Journal of Neurophysiology*, **87** 361–84.

Dodson HC (1997). Loss and survival of spiral ganglion neurons in the guinea pig after intracochlear perfusion with aminoglycosides. *Journal of Neurocytology*, **26**, 541–56.

Dreher B, Wang C, Turlejski KJ, Djavadian RL and Burke W (1996). Areas PMLS and 21a of cat visual cortex: two functionally distinct areas. *Cerebral Cortex*, **6**, 585–99.

Eggermont JJ (1985). Evoked potentials as indicators of auditory maturation. *Acta Otolaryngology (Stockholm)*, **421**, 41–7.

Eggermont JJ (1996). Differential maturation rates for response parameters in cat primary auditory cortex. *Auditory Neuroscience*, **2**, 309–27.

Ergenzinger ER, Glasier MM, Hahm JO and Pons TP (1998). Cortically induced thalamic plasticity in the primate somatosensory system. *Nature Neuroscience*, **1**, 226–9.

Falchier A, Clavagnier S, Barone P and Kennedy H (2002). Anatomical evidence of multimodal integration in primate striate cortex. *Journal of Neuroscience*, **22**, 5749–59.

Felix H and Hoffmann V (1985). Light and electron microscopic investigation of cochlear nerve specimens from profoundly deaf patients. *Acta Otolaryngology Supplement*, **423**, 67–72.

Fryauf-Bertschy H, Tyler RS, Kelsay DM, Gantz BJ and Woodworth GG (1997). Cochlear implant use by prelingually deafened children: the influences of age at implant and length of device use. *Journal of Speech, Language, and Hearing Research*, **40**, 183–99.

Gall CM (1993). Seizure-induced changes in neurotrophin expression: implications for epilepsy. *Experimental Neurology*, **124**, 150–66.

Giraud A, Price CJ, Graham JM, Truy E and Frackowiak RS (2001a). Cross-modal plasticity underpins language recovery after cochlear implantation. *Neuron*, **30**, 657–63.

Giraud AL, Price CJ, Graham JM and Frackowiak RS (2001b). Functional plasticity of language-related brain areas after cochlear implantation. *Brain*, **124**, 1307–16.

Giraud AL, Truy E and Frackowiak R (2001c). Imaging plasticity in cochlear implant patients. *Audiology Neuro-otology*, **6**, 381–93.

Harrison RV, Nagasawa A, Smith DW, Stanton S and Mount RJ (1991). Reorganization of auditory cortex after neonatal high frequency cochlear hearing loss. *Hearing Research*, **54**, 11–19.

Hartmann R, Shepherd RK, Heid S and Klinke R (1997). Response of the primary auditory cortex to electrical stimulation of the auditory nerve in the congenitally deaf white cat. *Hearing Research*, **112**, 115–33.

Hartmann R and Kral A (2004). Central responses to electrical stimulation. In: FG Zeng, RR Fay and AN Popper, eds *Springer Handbook of Auditory Research: Cochlear Inplants*. Springer New York, 213–218.

Heid S (1998). Morphologische Befunde am peripheren und zentralen auditorischen System der kongenital gehörlosen weißen Katze, [PhD Thesis]. Frankfurt am Main, J.W.Goethe University.

Heid S, Hartmann R and Klinke R (1998). A model for prelingual deafness, the congenitally deaf white cat—population statistics and degenerative changes. *Hearing Research*, **115**, 101–12.

Heid S, Jahnsiebert TK, Klinke R, Hartmann R and Langner G (1997). Afferent projection patterns in the auditory brainstem in normal and congenitally deaf white cats. *Hearing Research*, **110**, 191–9.

Heid S, Kral A, Ladewig V, Hartmann R and Klinke R (2000). Morphology of the cochlea and the spiral ganglion in cochlear-implanted congenitally deaf cats. *Proceedings of the Association for Research in Otolaryngology*, **23**, 229.

Hickmott PW and Constantine-Paton M (1997). Experimental down-regulation of the NMDA channel associated with synapse pruning. *Journal of Neurophysiology*, **78**, 1096–107.

Hubka P, Kral A, Klinke R (2004). Input desynchronization and impaired columnar activation in deprived auditory cortex revealed by independent component analysis. In: Syka J, Merezenich MM (eds). Plasticity and Signal Representation in the Auditory System. Springer Verlag, Berlin, 161–165.

Huttenlocher PR and Dabholkar AS (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology*, **387**, 167–78.

Innocenti GM, Berbel P and Clarke S (1988). Development of projections from auditory to visual areas in the cat. *Journal of Comparative Neurology*, **272**, 242–59.

Innocenti GM and Clarke S (1984). Bilateral transitory projection to visual areas from auditory cortex in kittens. *Brain Res*earch, **316**, 143–8.

Kaas JH, Florence SL and Jain N (1999). Subcortical contributions to massive cortical reorganizations. *Neuron*, **22**, 657–60.

Kapfer C, Seidl AH, Schweizer H and Grothe B (2002). Experience-dependent refinement of inhibitory inputs to auditory coincidence-detector neurons. *Nature Neuroscience*, **5**, 247–53.

Kennard MA (1938). Reorganization of motor function in the cerebral cortex of monkeys deprived of motor and premotor areas in infancy. *Journal of Neurophysiology*, **1**, 477–96.

Kiang NYS and Moxon EC (1972). Physiological considerations in artificial stimulation of the inner ear. *Annals of Otology, Rhinology and Laryngology*, **81**, 714–30.

Kilgard MP and Merzenich MM (1998). Cortical map reorganization enabled by nucleus basalis activity. *Science*, **279**, 1714–18.

Klinke R, Hartmann R, Heid S, Tillein J and Kral A (2001). Plastic changes in the auditory cortex of congenitally deaf cats following cochlear implantation. *Audiology and Neuro-otology*, **6**, 203–6.

Klinke R, Kral A, Heid S, Tillein J and Hartmann R (1999). Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation. *Science*, **285**, 1729–33.

Kral A, Hartmann R, Mortazavi D and Klinke R (1998). Spatial resolution of cochlear implants: the electrical field and excitation of auditory afferents. *Hearing Research*, **121**, 11–28.

Kral A, Tillein J, Hartmann R and Klinke R (1999). Monitoring of anaesthesia in neurophysiological experiments. *NeuroReport*, **10**, 781–7.

Kral A, Hartmann R, Tillein J, Heid S and Klinke R (2000). Congenital auditory deprivation reduces synaptic activity within the auditory cortex in a layer-specific manner. *Cereb Cortex*, **10**, 714–26.

Kral A, Hartmann R, Tillein J, Heid S and Klinke R (2001). Delayed maturation and sensitive periods in the auditory cortex. *Audiology and Neuro-Otolology*, **6**, 346–62.

Kral A, Hartmann R, Tillein J, Heid S and Klinke R (2002). Hearing after congenital deafness: central auditory plasticity and sensory deprivation. *Cerebral Cortex*, **12**, 797–807.

Kral A, Schroeder J-H, Klinke R and Engel AK (2003). Absence of cross-modal reorganization in the primary auditory cortex of congenitally deaf cats. *Experimental Brain Research* **153**, 605–613.

Kral A, Tillein J, Heid S, Hartmann R, Klinke R (2005). Postnatal cortical development in congenital auditory deprivation. *Cerebral Cortex* **15**:552–562.

Larkum ME, Zhu JJ and Sakmann B (1999). A new cellular mechanism for coupling inputs arriving at different cortical layers. *Nature*, **398**, 338–41.

Larsen SA and Kirchhoff TM (1992). Anatomical evidence of synaptic plasticity in the cochlear nuclei of white-deaf cats. *Experimental Neurology*, **115**, 151–7.

Leake PA, Hradek GT and Snyder RL (1999). Chronic electrical stimulation by a cochlear implant promotes survival of spiral ganglion neurons after neonatal deafness. *Journal of Comparative Neurology*, **412**, 543–62.

Lee DS, Lee JS, Oh SH, Kim SK, Kim JW, Chung JK, Lee MC and Kim CS (2001). Cross-modal plasticity and cochlear implants. *Nature*, **409**, 149–50.

Ma X and Suga N (2003). Augmentation of plasticity of the central auditory system by the basal forebrain and/or somatosensory cortex. *Journal of Neurophysiology*, **89**, 90–103.

Mair IWS (1973) Hereditary deafness in the white cat. *Acta Otolaryngology (Stockholm) Supplement*, **314**, 1–53.

Manunta Y and Edeline JM (1999). Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow-wave sleep. *European Journal of Neuroscience*, **11**, 2134–50.

McAllister AK, Katz LC and Lo DC (1996). Neurotrophin regulation of cortical dendritic growth requires activity. *Neuron*, **17**, 1057–64.

Meyer-Franke A, Wilkinson GA, Kruttgen A, Hu M, Munro E, Hanson MG, Jr., Reichardt LF and Barres BA (1998). Depolarization and cAMP elevation rapidly recruit TrkB to the plasma membrane of CNS neurons. *Neuron*, **21**, 681–93.

Mitzdorf U (1985). Current source-density method and application in cat cerebral cortex: investigation of evoked potentials and EEG phenomena. *Physiology Review*, **65**, 37–100.

Naito Y, Hirano S, Honjo I, Okazawa H, Ishizu K, Takahashi H, Fujiki N, Shiomi Y, Yonekura Y and Konishi J (1997). Sound-induced activation of auditory cortices in cochlear implant users with post- and prelingual deafness demonstrated by positron emission tomography. *Acta Oto-Laryngology*, **117**, 490–6.

O'Kusky J and Colonnier M (1982). Postnatal changes in the number of neurons and synapses in the visual cortex (area 17) of the macaque monkey: a stereological analysis in normal and monocularly deprived animals. *Journal of Comparative Neurology*, **210**, 291–306.

O'Kusky JR (1985). Synapse elimination in the developing visual cortex: a morphometric analysis in normal and dark-reared cats. *Brain Res*earch, **354**, 81–91.

Pantev C and Lutkenhoner B (2000). Magnetoencephalographic studies of functional organization and plasticity of the human auditory cortex. *Journal of Clinical Neurophysiology*, **17**, 130–42.

Ponton CW, Don M, Eggermont JJ, Waring MD, Kwong B and Masuda A (1996a). Auditory system plasticity in children after long periods of complete deafness. *NeuroReport*, **8**, 61–5.

Ponton CW, Don M, Eggermont JJ, Waring MD and Masuda A (1996b). Maturation of human cortical auditory function: differences between normal-hearing children and children with cochlear implants. *Ear and Hearing*, **17**, 430–7.

Ponton CW and Eggermont JJ (2001). Of kittens and kids: Altered cortical maturation following profound deafness and cochlear implant use. *Audiology and Neuro-otology*, **6**, 363–80.

Ponton CW, Moore JK and Eggermont JJ (1999). Prolonged deafness limits auditory system developmental plasticity: evidence from an evoked potentials study in children with cochlear implants. *Scandinavian Audiology Supplement*, **51**, 13–22.

Rebillard G, Carlier E, Rebillard M and Pujol R (1977). Enhancement of visual responses on the primary auditory cortex of the cat after an early destruction of cochlear receptors. *Brain Research*, **129**, 162–4.

Rebillard G, Rebillard M and Pujol R (1980). Factors affecting the recording of visual-evoked potentials from the deaf cat primary auditory cortex (AI). *Brain Res*earch, **188**, 252–4.

Recanzone GH, Schreiner CE and Merzenich MM (1993). Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *Journal of Neuroscience*, **13**, 87–103.

Redd EE, Pongstaporn T, Ryugo DK (2000). The effects of congenital deafness on auditory nerve synapses and globular bushy cells in cats. *Hearing Resarch* **147**: 160–174.

Robertson D and Irvine DR (1989). Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *Journal of Comparative Neurology*, **282**, 456–71.

Ryugo DK, Pongstaporn T, Huchton DM and Niparko JK (1997). Ultrastructural analysis of primary endings in deaf white cats: morphologic alterations in endbulbs of Held. *Journal of Comparative Neurology*, **385**, 230–44.

Ryugo DK, Rosenbaum BT, Kim PJ, Niparko JK and Saada AA (1998). Single unit recordings in the auditory nerve of congenitally deaf white cats: Morphological correlates in the cochlea and cochlear nucleus. *Journal of Comparative Neurology*, **397**, 532–48.

Saada AA, Niparko JK and Ryugo DK (1996). Morphological changes in the cochlear nucleus of congenitally deaf white cats. *Brain Res*earch, **736**, 315–28.

Schroeder CE, Lindsley RW, Specht C, Marcovici A, Smiley JF and Javitt DC (2001) Somatosensory input to auditory association cortex in the macaque monkey. *Journal of Neurophysiology*, **85**, 1322–7.

Schwartz DR, Schacht J, Miller JM, Frey K and Altschuler RA (1993). Chronic electrical stimulation reverses deafness-related depression of electrically evoked 2-deoxyglucose activity in the guinea pig inferior colliculus. *Hearing Research*, **70**, 243–9.

Segal I, Korkotian I and Murphy DD (2000). Dendritic spine formation and pruning: common cellular mechanisms? *Trends in Neuroscience*, **23**, 53–7.

Sharma A, Dorman And MF and Spahr AJ (2002a). A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear and Hearing*, **23**, 532–9.

Sharma A, Dorman M, Spahr A and Todd NW (2002c). Early cochlear implantation in children allows normal development of central auditory pathways. *Annals of Otology, Rhinology and Laryngology Supplement*, **189**, 38–41.

Sharma A, Dorman MF and Spahr AJ (2002b). Rapid development of cortical auditory-evoked potentials after early cochlear implantation. *NeuroReport*, **13**, 1365–8.

Shepherd RK and Hardie NA (2001). Deafness-induced changes in the auditory pathway: implications for cochlear implants. *Audiology and Neuro-Otology*, **6**, 305–18.

Snyder RL, Rebscher SJ, Cao K, Leake PA and Kelly K (1990). Chronic intracochlear electrical stimulation in the neonatally deafened cat .1. Expansion of central representation. *Hearing Research*, **50**, 7–34.

Spear PD (1991). Functions of extrastriate visual cortex in non-primate species. In: J Cronly-Dillon, ed. *The Neural Basis of Visual Function, vol. 4: Vision and Visual Dysfunction*, pp. 339–69. Macmillan, Basingstoke.

Stanton SG and Harrison RV (1996). Abnormal cochleotopic organization in the auditory cortex of cats reared in a frequency augmented environment. *Auditory Neuroscience*, **2**, 97–107.

Stewart DL and Starr A (1970). Absence of visually influenced cells in auditory cortex of normal and congenitally deaf cats. *Experimental Neurology*, **28**, 525–8.

Suga N, Gao E, Zhang Y, Ma X and Olsen JF (2000). The corticofugal system for hearing: recent progress. *Proceedings of the National Acadamy of Science of the United States of America*, **97**, 11807–14.

Tyler RS, Teagle HFB, Kelsay DMR, Gantz BJ, Woodworth GG and Parkinson AJ (2000). Speech perception by prelingually deaf children after six years of cochlear implant use: effects of age at implantation. *Annals of Otology, Rhinology and Laryngology*, **109**, 82–4.

Vasama JP and Linthicum FH Jr (2000). Idiopathic sudden sensorineural hearing loss: temporal bone histopathologic study. *Annals of Otology, Rhinology and Laryngology*, **109**, 527–32.

Wallhäuser E and Scheich H (1987). Auditory imprinting leads to differential 2-deoxyglucose uptake and dendritic spine loss in the chick rostral forebrain. *Developmental Brain Research*, **31**, 29–44.

Winfield DA (1981). The postnatal development of synapses in the visual cortex of the cat and the effects of eyelid closure. *Brain Research*, **206** 166–71.

Wurth NN (1999). Vergleichende Morphologie der Neurone im Primären Auditorischen Cortex der Kongenital Gehörlosen Weißen Katze. Thesis, J.W. Goethe-Universität, Frankfurt am Main, Germany.

Yaka R, Yinon U and Wollberg Z (1999). Auditory activation of cortical visual areas in cats after early visual deprivation. *European Journal of Neuroscience*, **11**, 1301–12.

Zafra F, Lindholm D, Castren E, Hartikka J and Thoenen H (1992). Regulation of brain-derived neurotrophic factor and nerve growth factor mRNA in primary cultures of hippocampal neurons and astrocytes. *Journal of Neuroscience* **12**, 4793–9.

Zhang LI, Bao S and Merzenich MM (2002). Disruption of primary auditory cortex by synchronous auditory inputs during a critical period. *Proceedings of the National Acadamy of Science of the United States of America*, **99**, 2309–14.