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CHAPTER 18

Cochlear implants: cortical plasticity in congenital deprivation

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Abstract: Congenital auditory deprivation (deafness) leads to a dysfunctional intrinsic cortical microcircuitry. This chapter reviews these deficits with a particular emphasis on layer-specific activity within the primary auditory cortex. Evidence for a delay in activation of supragranular layers and reduction in activity in infragranular layers is discussed. Such deficits indicate the incompetence of the primary auditory cortex to not only properly process thalamic input and generate output within the infragranular layers, but also incorporate top-down modulations from higher order auditory cortex into the processing within primary auditory cortex. Such deficits are the consequence of a misguided postnatal development. Maturation of primary auditory cortex in deaf animals shows evidence of a developmental delay and further alterations in gross synaptic currents, spread of activation, and morphology of local field potentials recorded at the cortical surface. Additionally, degenerative changes can be observed. When hearing is initiated early in life (e.g., by chronic cochlear-implant stimulation), many of these deficits are counterbalanced. However, plasticity of the auditory cortex decreases with increasing age, so that a sensitive period for plastic adaptation can be demonstrated within the second to sixth months of life in the deaf cat. Potential molecular mechanisms of the existence of sensitive period are discussed. Data from animal research may be compared to electroencephalographic data obtained from cochlear-implanted congenitally deaf children. After cochlear implantation in humans, three phases of plastic adaptation can be observed: a fast one, taking place within the first few weeks after implantation, showing no sensitive period; a slower one, taking place within the first months after implantation (a sensitive period up to 4 years of age); and possibly a third, and the longest one, related to increasing activation of higher order cortical areas.

Keywords: sensitive period; layer-specific activity; top-down projection; current source density; development; maturation; auditory cortex

Introduction

Cochlear implants (Fig. 1) are the most successful of all neuroprosthetic devices. They consist of an electrode array placed on a thin silastic carrier (implanted in the cochlea), a subcutaneous receiver (implanted in the skull behind the ear), and a microphone with a sound or speech processor (worn extracorporally). The processor receives the signal from the microphone, preprocesses it using the selected coding strategy, and transmits the

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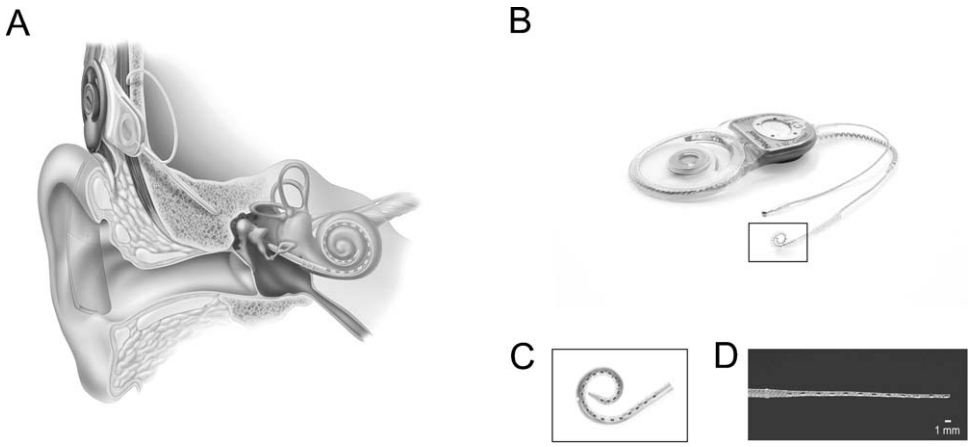

Fig. 1. A commercial cochlear implant device consisting of an extracorporal sound processor with a microphone and an attached transmitter coil (A, courtesy of Cochlear Corp., Melbourne, Australia). This device transmits signals magnetically to a subcutaneously located receiver unit (B, Cochlear Corp., Melbourne, Australia) connected to an indifferent extracochlear electrode and an intracochlear electrode array. The intracochlear electrode arrays are either precurved with a stand (C, Cochlear Corp., Melbourne, Australia) or straight (D, MedEl Company, Innsbruck, Austria).

information through HF transmission via a coil onto the subcutaneous receiver. This then relays the signals to the stimulating electrodes. The stimulation array of the cochlear implant is inserted into the scala tympani through either the round window or a cochleostomy.

Cochlear implants are used to treat hearing loss caused by a nonfunctional organ of Corti. Nonetheless, the indication of a cochlear implantation has been expanding over the last decade, now sometimes also including individuals with residual hearing and lack of benefit from conventional high-power hearing aids (von Ilberg et al., 1999; Kiefer et al., 2004), individuals suffering from strong tinnitus (Thedinger et al., 1985; McKerrow et al., 1991; Dauman et al., 1993; Ito and Sakakihara, 1994; Tyler, 1995; Ruckenstein et al., 2001), and individuals with the so-called auditory neuropathy (Miyamoto et al., 1999; Trautwein et al., 2000; Shallop et al., 2001; Sininger and Trautwein, 2002).

"Electric hearing" is also a suitable tool to investigate effects of auditory deprivation and developmental plasticity. Functional consequences of auditory deprivation cannot be investigated as easily as in visual deprivation: simple suturing of the ear canals does not suffice to block all hearing. The thresholds rarely increase by more than 40 dB, and bone conduction is not attenuated at all. Consequently, mechanical manipulations on the external meatus cannot prevent hearing experience. Surgical destruction of the middle ear also does not suffice, as it does not affect bone conduction. Consequently, sounds from swallowing, chewing, breathing, sneezing, coughing, but most importantly own vocalizations are not attenuated by such intervention. Cochlear destructions, like the frequently used cochlear ablation, are irreversible (for detailed comparison on the different deprivation models see Kral et al., 2001; Syka, 2002).

The need for a neurophysiological model of congenital auditory deprivation arose with the introduction of cochlear implantation. The first models of auditory deprivation were based on pharmacological destruction of the inner ear; functional data on a deprived auditory system could be gathered using electrical stimulation of the surviving fibers of the auditory nerve. Later, congenitally deaf animal strains have been introduced to this area of research.

Electrical stimulation of the auditory nerve

Electrical stimulation of the auditory nerve induces a pattern of activity in the afferent auditory system that differs from that induced by acoustic stimulation of a hearing cochlea. Destruction or degeneration of hair cells eliminates spontaneous activity in the auditory nerve (Hartmann et al., 1984). Electrical stimulation is additionally characterized by

- *Lack of precise spatial information* — a "beam forming" is possible in electrical stimulation of the auditory nerve, but the resulting tuning curves are much less sharp than with acoustic stimulation (Kral et al., 1998).
- *Lack of stochasticity* — electrically evoked action potentials express much less temporal jitter than the action potentials evoked by acoustic stimuli in a hearing cochlea, resulting in a "hypersynchronization" of the evoked activity to the electrical stimulation. This has several unwanted effects including steep loudness growth. Despite of high-frequency stimulation in commercial cochlear implants where individual stimulation pulses can fall into the refractory period of the fibers, and despite of the attempts to introduce stochasticity in the elicited firing pattern by adding subthreshold electrical noise, the stochasticity of auditory nerve firing pattern is less in cochlear implants patients than in hearing individuals (Hartmann et al., 1984; Rubinstein et al., 1999).
- *Compressed dynamic range* — responses of single auditory nerve fibers to electrical stimulation saturate within 3–10 dB above threshold. This represents a substantial collapse of the normal dynamic range of 40–80 dB in auditory nerve fibers. Consequently, the loudness range is substantially compressed in cochlear implant users as compared to normal acoustic hearing (review in Hartmann and Klinke, 1990).

Plasticity, development, and deprivation

Cochlear implants provide a way to obtain information about the function of the auditory system that has been deaf for a certain time. The deaf ear can be chronically stimulated electrically by using cochlear implants making it possible to study the central auditory plasticity.

Central reorganizations induced by cochlear implants involve several different types of plasticity:

1. Reorganization of the auditory system can be induced in hearing-experienced individuals (animals and humans) who became deaf as adults and received a cochlear implant after a certain period of deafness. To compensate for deafness-induced degenerative changes in the auditory system, these individuals have to undergo plastic reorganization to adapt to the abnormal characteristics of the neural activity evoked by the cochlear implant. This type of plastic reorganization is similar to other forms of learning-induced plasticity with the difference that the reorganization is preceded by a period of deprivation and is more extensive because the evoked activity becomes different from that evoked by sound during the period of hearing. The "interpretation" of the new stimulation mode has to be newly learned.
2. Previous studies have consistently shown that the development of the central auditory system is shaped by acoustic experience (for review on owls spatial orientation, see Knudsen, 2004; for review on language-related aspects, see Skuse, 1993; Ruben, 1997; Kuhl, 2004; for review on auditory aspects and neurophysiology in mammals, see Kral et al., 2001; Syka, 2002). Since the auditory system in the congenitally deaf individual does not have any input, the shaping of the auditory system through experience does not occur and the normal adaptation to the acoustic environment does not take place (review in Kral et al., 2001; Hartmann and Kral, 2004). Such an acoustically naïve auditory system has to undergo additional adaptations after cochlear implantation. It has to catch up with the activity-dependent maturation that the auditory system has missed during previous development. Therefore, the plasticity in a naive auditory system cannot be functionally compared to plasticity in an experienced auditory system. The term *developmental plasticity* will be used for this type of plasticity in the following text.

Postnatal development of a naïve auditory system

Auditory deprivation induces many changes in the central auditory nervous system. These can be divided into dystrophic changes of the morphology of neurons in different nuclei of the auditory system and changes in the connectivity, eventually leading to deficits in functional properties of the central auditory system. These changes are usually assumed to occur in the ascending auditory pathways including the auditory cerebral cortices, but changes may also occur in descending systems.

Degenerative changes in the auditory nervous system have been described for neonatally deafened and congenitally deaf animals. Dystrophic morphological abnormalities in the central auditory system of naïve animals include changes in the structure of the neuronal body and synaptic endings (for details, see recent review articles, Kral et al., 2001; Hartmann and Kral, 2004; Middlebrooks et al., 2005). The main afferent projections in the auditory system are only marginally affected by congenital auditory deprivation (Heid et al., 1997). The synaptic changes, which have been investigated most extensively in the cochlear nucleus (Hultcrantz et al., 1991; Larsen and Kirchhoff, 1992; Lustig et al., 1994; Saada et al., 1996; Ryugo et al., 1997), include dystrophic and hypertrophic changes. Reductions in synaptic numbers and densities have been demonstrated in the midbrain of neonatally deafened animals (Hardie et al., 1998).

Functional changes in the different nuclei of the ascending auditory pathways including the different regions of the cerebral auditory cortex have been studied using electrical stimulation of auditory nerve fibers in the cochlea of neonatally deaf and deafened animals.

For experiments in animals, the availability of suitable animal species is limited. Such animals should be completely and congenitally deaf with well-preserved auditory nerve.

> There are genetically modified rodent strains with hearing loss (reviewed in Kiernan and Steel, 2000), but they are often not completely deaf at birth. Investigations of central deficits from auditory deprivation are now dominated by two models: neonatally deafened animals and congenitally deaf species such as the deaf white cat (review e.g., in Hartmann and Kral, 2004). Both these models have advantages and disadvantages. In neonatally deafened animals, the destruction of the inner ear is achieved by systemic application of ototoxic substances during the phase of hearing acquisition. The advantage of neonatally deafened animals is the easy availability, and the disadvantage is the pronounced and rapid degeneration of spiral ganglion cells (cell loss from 50–90% of normal counts after several weeks to months of deafness, see Leake-Jones et al., 1982; Leake et al., 1987, 1999; Leake and Hradek, 1988; Dodson, 1997a, b).
>
> It is an important advantage of congenitally deaf strains that some of them show a slow degeneration of spiral ganglion cells, comparable to human congenital deafness. The disadvantage of congenitally deaf animals is their lesser availability because their litters are often small.
>
> In the congenitally deaf (white) cats (CDCs), all hair cells are lost spontaneously prior to hearing onset (Heid et al., 1998). The cochlea shows the picture of Scheibe dysplasia, with preserved bony structure, with preserved auditory nerve and spiral ganglion, but with dystrophic and degenerative changes in the scala media (including a collapse of the Reissner's membrane, a retraction of the tectorial membrane, and some other more subtle deficits). Although there is some degeneration in the spiral ganglion, the degeneration progresses much slower than in neonatally deafened animals. Most importantly, in the first halfturn of the cochlea (where a cochlear implant can be inserted in a cat, Kral et al., 1998), there is no significant loss of spiral ganglion cells up to the age of 2 years (Heid et al., 1998). This means that in contrast to neonatal deafening, no degeneration of spiral ganglion cells can be observed at the site of most effective electrical stimulation, thus allowing studies of central auditory evoked responses elicited by cochlear implant stimulation in congenitally deaf cats.

Functional changes in the afferent auditory system were not prominent in neonatally or congenitally deaf animals. In the auditory midbrain, several parameters including poststimulus time

histograms, maximum following frequency and entrainment, as well as latencies or amplitudes of the responses were not significantly affected by the absence of auditory experience (Snyder et al., 1990, 1991). Reductions in occurrence of long-latency responses in the midbrain were observed (Snyder et al., 1991). Other investigators also described reductions in the temporal jitter of the responses (Shepherd et al., 1999).

Greater abnormalities were observed in the auditory cortex, where auditory deprivation induced numerous and extensive processing deficits. In the adult auditory cortex, the representations of the stimulated auditory partition changed. Although a rudimentary cochleotopy could be demonstrated in congenitally deaf cats (Hartmann et al., 1997), the cochleotopy became progressively more smeared with the duration of the absence of auditory experience in neonatally deafened animals (Raggio and Schreiner, 1999), indicating a degenerative process in the spatial organization of the auditory cortex acting over the time of complete auditory deprivation. It has to be considered that the process of degeneration of the spiral ganglion cells in neonatally deafened animals may contribute to this smearing of the cochleotopic gradient (Dodson, 1997a, b; Leake et al., 1999; Dodson and Mohuiddin, 2000). Other characteristics of responses to simple electrical stimuli from cells in the primary auditory cortex (field A1), like the dynamic range, latencies of responses, and post-stimulus time histograms, were similar in the cortex of deaf and hearing cats (Raggio and Schreiner, 1994). However, spontaneous activity was slightly, but significantly increased in the field A1 of congenitally deaf cats (Fig. 2, Kral et al., 2003).

Current source density analysis in deaf auditory cortex

Further deafness-induced deficits in the cortical microcircuitry have been observed in congenitally deaf cats using the current source density (CSD) method. The CSD analysis makes it possible to describe the activation of the auditory cortex in a layer-specific manner.

> The current density analysis is based on Maxwell's electrical field theory and has been adapted for use in neurophysiology by Walter Pitts and later by Nicholson and Freeman (Pitts, 1952; Nicholson and Freeman, 1975). Applied to the cerebral cortex, the method relies on measurements of local field potentials in different cortical layers with microelectrodes (Fig. 3). From these signals, the second spatial derivative

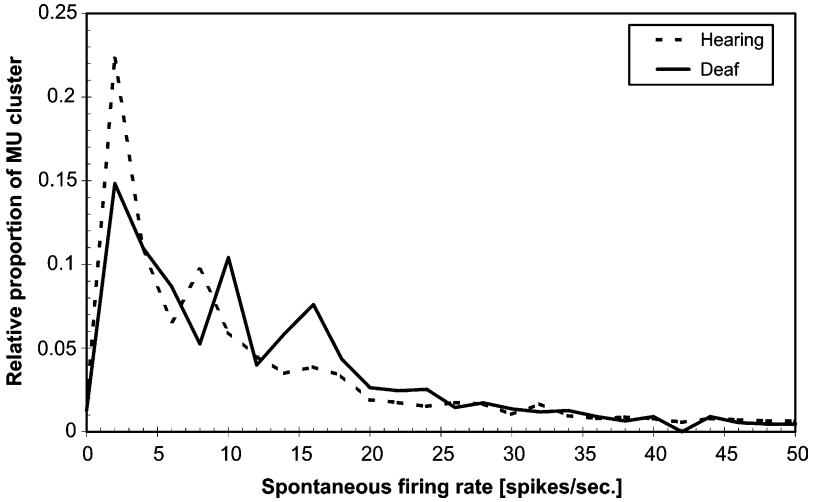

Fig. 2. Distribution of cortical spontaneous activity in halothane-anesthetized adult hearing controls (dashed) and congenitally deaf cats. Congenitally deaf cats show higher spontaneous activity (median in controls = 8.0 spikes/s, median in deaf cats = 9.8 spikes/s, χ^2 test, $\alpha = 1\%$, reprinted with permission from Kral et al., 2003).

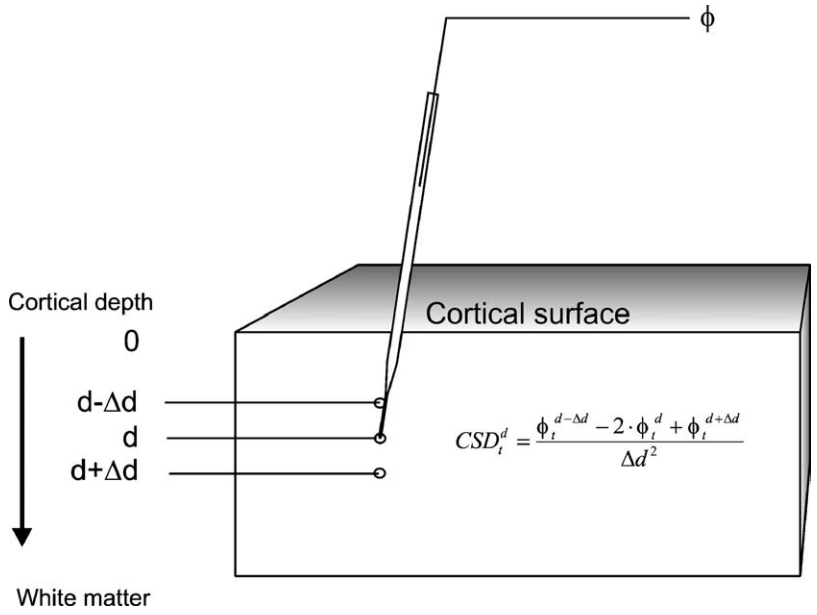

Fig. 3. One-dimensional CSD signals represent the second spatial derivative of the local field potentials recorded during a penetration through the cortex perpendicular to the cortical surface (modified with permission from Kral et al., 2000).

multiplied by a resistivity tensor is computed to obtain the so-called *CSD*.

The CSD signals are the effect of synaptic currents in close proximity of the tips of the recording microelectrodes. For example, once α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors are activated, a sodium channel opens and sodium flows into the cell (the electrical current is physically oriented into the cell, *inward current*), leaving a *current sink* in the extracellular space. As the inward current depolarizes the membrane of the neuron ("discharges" the capacitor), it sets free the positive ions originally attracted to the extracellular side of the neuronal membrane by the membrane potential. The positive ions become mobile and detach from the membrane, causing a *current source* in the extracellular space (current oriented out of the cell, *outward current*). The current source balances the current sink and neutralizes the extracellular space. However, this *passive return current* is distributed over larger portions of the neuronal membrane near the activated synapse and is therefore locally of smaller magnitude. Depending on the method of recordings and filtering the original signals, these passive return currents may be less obvious in the computed CSD profiles. Inhibitory synaptic currents, in contrast, are caused by the outflow of positive ions (potassium) or inflow of negative ions (chloride), thus causing a current source in the extracellular space (provided a resting transmembrane potential).

One-dimensional CSD analysis reveals only the current sinks and sources that are the consequence of the currents flowing perpendicularly to the electrode penetration. Consequently, the CSD signals obtained from electrode penetrations perpendicular to the cortical surface will in fact reveal the extracellular synaptic currents of cells with elongated structure running in parallel to the electrode penetration. In the cortex, penetrations oriented perpendicularly to the cortical surface will therefore mainly reveal synaptic currents from pyramidal cells that are large, oriented parallel to the electrode penetration and to each other, and are arranged regularly. Smaller cells with globular architecture and less regular arrangement in individual cortical layers (e.g., stellate cells) will be less represented in these signals. Owing to the fact that passive currents are

distributed over larger portions of neuronal membranes and in all three space dimensions, they produce smaller one-dimensional CSD signals than "true" (active) synaptic currents that are much more localized.

From a theoretical point of view, the local field potentials used for calculation of the CSD should be recorded simultaneously. An advantage of a simultaneous recording is that single-sweep data can be used for its computation, thus allowing a trial-to-trial analysis. With such an approach, the differences in the impedance of individual electrodes have to be considered; otherwise, they would introduce errors in the estimation of the current source densities. Additionally, the electrode shank affects the shape of the electrical field around the electrode (if of different impedance than the surrounding tissue).

An often-used alternative is to record local field potentials with an individual electrode successively located at different recording positions and perform the calculation of current source densities off line (e.g., Friauf and Shatz, 1991; Cruikshank et al., 2002). This method only allows CSD computation on averaged local field potentials as the average represents the invariant part of the evoked response, and thus the shift in time between individual recording positions does not invoke a bias into the data.

Glass microelectrodes with very narrow shanks can be used for recording, minimizing the tissue trauma and the influence of the electrode on the geometry of the electrical field, which confers an advantage. Using glass microelectrodes, iontophoretic application of dyes is possible and thus exact reconstructions of the electrode penetration within the tissue become available. For technical details of the method compare e.g. Nicholson and Freeman (1975), Mitzdorf (1985), and Somogyvari et al. (2005). In our laboratories both techniques are used, but the data reviewed here rely solely on the single-electrode technique.

The CSD method allows an effective assessment of the synaptic activity in different layers of the auditory cortex. In contrast to intracellular recordings, the current CSD method gives information about several hundreds of synapses at the same time and by that undersampling of the synaptic activity is avoided.

1. Extracellular synaptic currents have a different shape when compared to intracellularly recorded synaptic currents. Spikes, in the first approximation, appear like a temporal derivative of the time function of the spike recorded intracellularly. Synaptic currents are most probably less "distorted."
2. The sensitivity of the CSD method is lower than that of intracellular recordings or whole-cell patch clamp regarding the number of active synapses. The results of the CSD method represents the activity in hundreds of active synapses mixed together in a single signal. The computation of the CSD therefore represents the average synaptic currents at the recording position.

It is evident that the pattern of activity obtained with this method is specific for individual cortical layers (Fig. 4). The method produces well-reproducible results, and the activity in the different layers (like the borders of layer IV) can be distinguished in the waveform of CSD signals. Penetrations with smaller distances between recording positions reveal additional sink and sources that are hidden in the more course penetrations (Kral and Hartmann, unpublished data). Recording steps from 50 μm to 300–500 μm have been used in different studies. The finer the steps, the more spatial and temporal details can be obtained from the CSD signals.

To be able to determine CSD signals from functionally corresponding cortical positions in different animals, the cortical area has to be mapped first. This can be done using local field potentials recorded from the cortical surface with high-impedance glass microelectrodes. The resulting functional maps can be quantitatively analyzed, and the location with largest responses can be determined (region of interest, ROI, size: 1 mm^2). In the studies reviewed here, the signals used for CSD computation and single-unit activity were recorded in such defined ROIs.

Activity in the auditory cortex of congenitally deaf cats was analyzed using the above method and compared to hearing controls stimulated

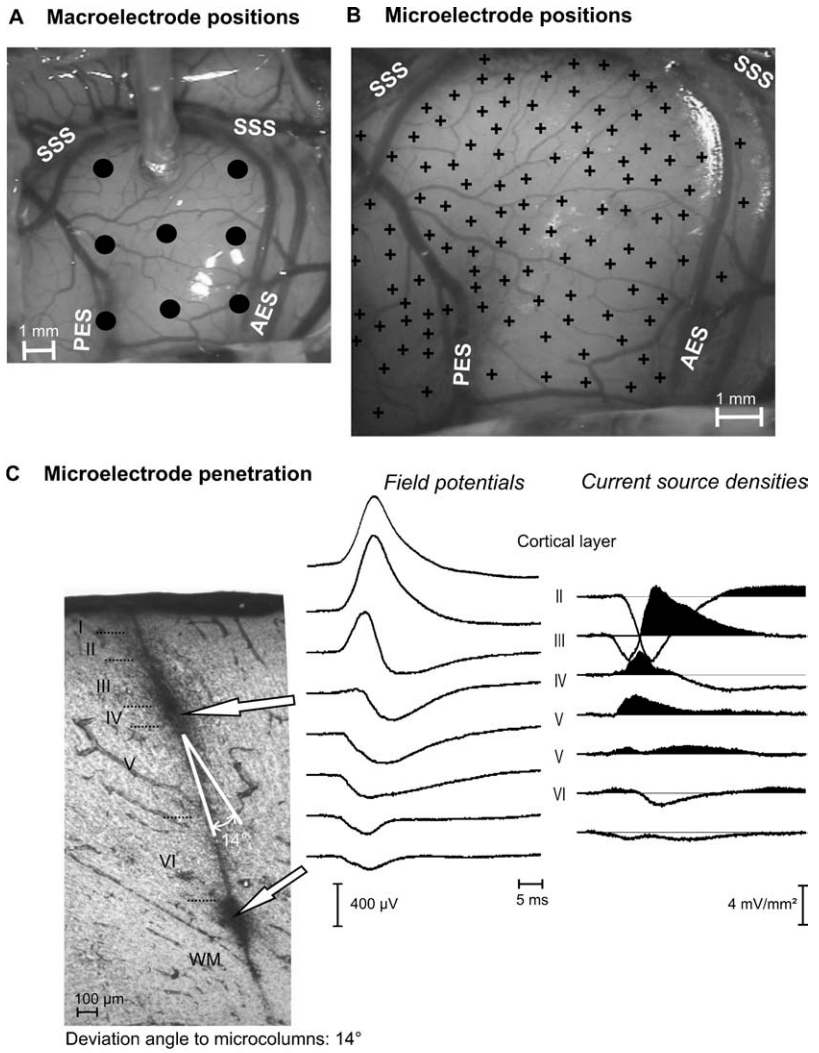

Fig. 4. Neurophysiological approach for determining CSD signals. First, lowest cortical threshold were determined using local field potentials recorded with low-impedance electrodes at a 3×3 recording grid at the field A1 (A). At 10 dB above the lowest thresholds, the primary auditory cortex was mapped using local field potentials recorded at the cortical surface with glass microelectrodes ($Z = 6$ MΩ) at 100–170 recording positions (B). At the spot with largest responses, a region of interest (ROI) with 1 mm^2 was defined and there the cortex was penetrated at a grid of 2×3 positions (500 µm spaced). Two recording positions were marked by iontophoretic application of horseradish peroxidase and the penetration was histologically reconstructed after the experiment (C). Recorded local field potentials could then be assigned to cortical layers and CSD signals could be computed (sinks are filled; reprinted with permission from Kral et al., 2005).

electrically (Fig. 5). Such comparison revealed numerous deficits in the activation of the auditory cortex of congenitally deaf cats.

A significant decrease was shown in the mean amplitude of gross synaptic currents, both expressed in the maximum current of each sink and in the temporal integrals of the sinks (Kral et al., 2000). These results may be caused by desynchronization of synaptic activity, a reduction of the number of activated synapses, or a reduction in the amplitude of the individual synaptic currents in the primary auditory cortex of congenitally deaf cats.

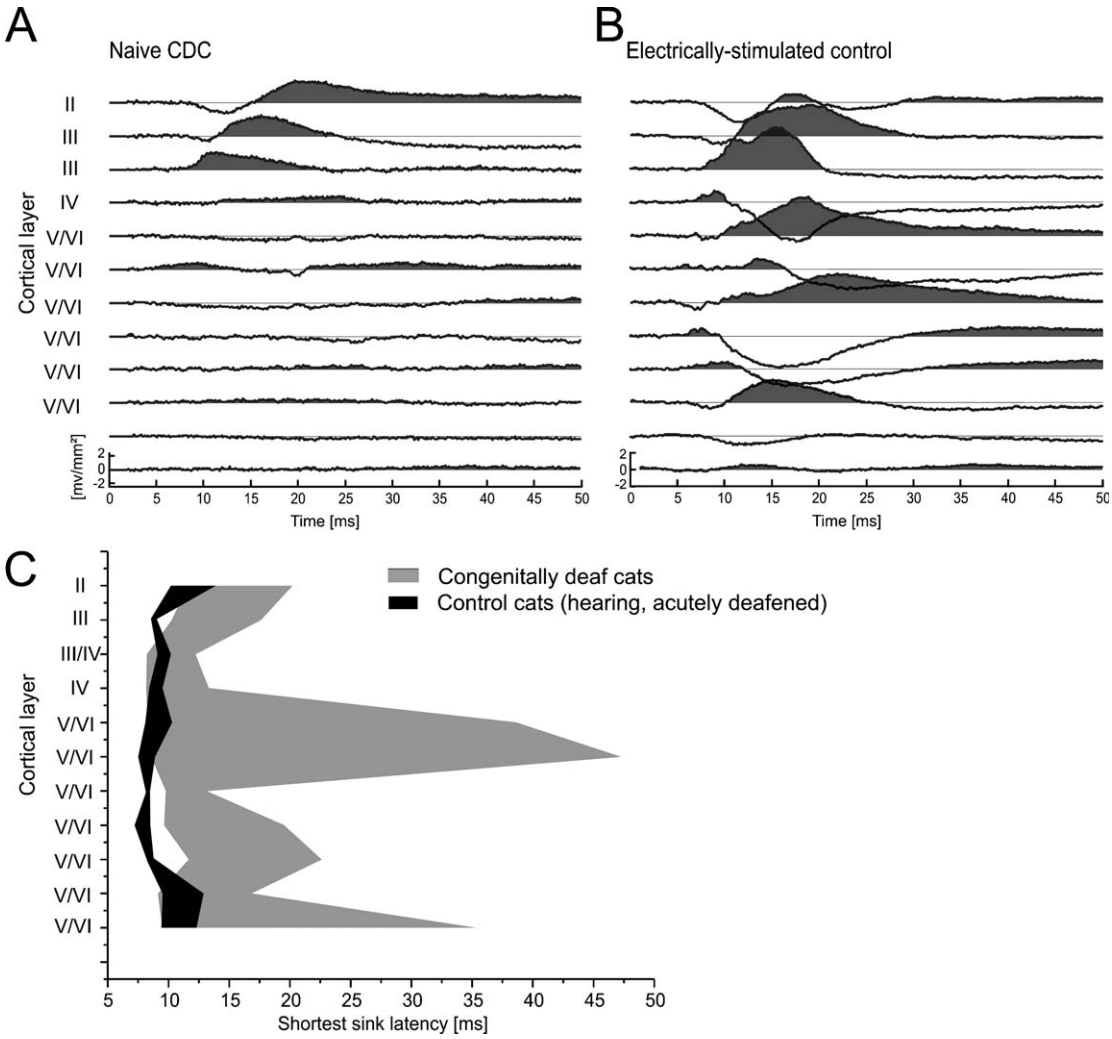

Fig. 5. Representative examples of CSD signals in naïve adult deaf cats (A) and electrically stimulated controls (B), sinks are filled. The amplitudes of the signals in deaf animals are significantly smaller (Wilcoxon–Mann–Whitney test, $\alpha = 5\%$) and concentrated to mainly the supragranular layers. The shortest latencies evaluated in each layer separately were significantly delayed in congenitally deaf cats in supragranular and infragranular layers and no difference was found in layer IV (C, data from Kral et al., 2000).

Desynchronization of neuronal activity has further been documented by a less synchronous activation of the cortical column in congenitally deaf cats (Fig. 5). The supragranular layers in congenitally deaf cats were activated with significant delays not found in hearing controls. A delay in activation of cells in the supragranular layers in relation to cells in layer IV may have the consequence of desynchronization of the excitatory drive on pyramidal cells of layer V (Larkum et al., 1999). This in turn may prevent an appropriate activation of these cells, and thus impair the function of the intrinsic cortical microcircuitry in cortical "modules" (columns), affecting activity in infragranular layers. Reductions of synaptic activity were also found in the infragranular cortical layers V and VI in congenitally deaf cats (Kral et al., 2000). These layers are targets of descending projections from the higher auditory cortex, and reductions in the activity in layer V and VI further

indicate reduced input from descending cortico-cortical projections. In congenitally deaf animals, activity in field A1 was restricted to a shorter interval after the stimulus. This is considered a consequence of the above-described functional disintegration of the activity in the cortical module. Long-latency activity was also reduced in deaf animals. Comparisons in source amplitudes between deaf and hearing animals revealed a significant reduction in layers III and IV in the field A1 of the deaf animals (Hubka et al., 2004; Kral et al., 2005). Inhibitory synapses are most abundant in layer I, with layers II–IV following (Prieto et al., 1994a, b). This result therefore indicates reductions in the synaptic function within layers III and IV of congenitally deaf cats. Layers III and IV are essential for cortical propagation of activity from thalamus to supragranular layers — according to some authors they perform a gating function (Rozas et al., 2001). This gating develops during postnatal life, shaped by experience. Accordingly in the visual system, neonatal deprivation was shown to increase the sensitivity of layer IV (Maffei et al., 2004). Down-regulation of inhibition in this layer, as indicated by the above data in the auditory cortex of deaf animals, thus corresponds to the findings in the visual system.

The deficits that are revealed using the CSD method are not prominently expressed in surface-recorded local field potentials, which are dominated by supragranular activity. However, the amplitude of the negative wave Nb in the evoked potentials recorded from the surface of the cerebral cortex is significantly reduced in adult congenitally deaf cats. The wave P1 is reduced in amplitude and its latency is prolonged in adult congenitally deaf cats (Klinke et al., 1999; Kral et al., 2005).

These processing deficits may have several causes. They may be caused by degenerative processes in the auditory cortex due to inactivity. Alternatively, a misguided developmental sequence may lead to a dysfunctionality of the auditory cortex. Last but not least, recruitment for another function is the last option; this may lead to a reduced possibility for activation of the primary auditory cortex by auditory input.

The last mentioned option can, however, be ruled out for the following reasons: If the cells in the primary auditory cortex were recruited for function other than the normal one, it would be expected that the more active synapses would prevail in competition for synaptic space and those that normally receive input from sources that are inactive (the auditory thalamus) would be suppressed. The most probable consequence of such a condition would be an increase in auditory activation thresholds. However, currently available data show that this is not the case, neither in congenitally deaf nor in neonatally deafened animals (Raggio and Schreiner, 1999; Kral et al., 2005). In congenitally deaf cats, the thresholds for activation of the auditory cortex via the lemniscal pathway (via a cochlear implant) were not higher than those in hearing controls; on the contrary, they were significantly lower (Kral et al., 2005). This "hypersensitivity" to auditory inputs most probably appeared at the central, possibly thalamocortical level (for arguments see Kral et al., 2005; for possible mechanisms see Kotak et al., 2005).

Evidences of cross-modal reorganization of the higher order auditory cortex by the visual inputs have been demonstrated in many human studies (e.g.,Nishimura et al., 1999; Petitto et al., 2000; Finney et al., 2001). Reorganization did occur not only for linguistic visual material, but also for non-linguistic, moving visual stimuli (Finney et al., 2001, 2003). Nonetheless, different cortical areas differ in their receptiveness for cross-modal reorganization. Only a reorganization of higher order auditory areas has been clearly demonstrated, and cross-modal reorganizations of the primary areas have not been unambiguously shown in these studies.

Previously, Stewart and Starr investigated visual responses in the primary auditory cortex of awake congenitally deaf cats with visual flashes. They did not obtain any multiunit responses in field A1 (Stewart and Starr, 1970). However, later studies claimed to have found visually evoked local field potentials also in the primary auditory cortex of anaesthetized congenitally deaf cats (Rebillard et al., 1977, 1980). To resolve this discrepancy, we undertook a study using controlled visual stimulation (Kral et al., 2003).

> In this study on lightly halothane-anaesthetized cats eye refraction was assessed and

corrected with contact lenses to assure a sharp picture on the retina. Backprojection of the fovea on the screen was used to assure accurate stimulus presentation site. Visual flashes were presented at the fovea, followed by presentation of phase-reversal gratings (inducing the impression of a motion) of different spatial frequencies and orientations. These stimuli are effective in activating both the ventral and the dorsal streams of cortical visual processing, as they include both pattern and movement. To stimulate the peripheral parts of the visual field, light bars of different orientations, movement directions, and speed were manually presented in the periphery of the visual field.

Both local field potentials and unit activity were recorded in all cortical layers of field A1. From all cell clusters recorded in field A1, 98% did not show any modulation of spontaneous activity by the visual stimulus in deaf cats. In the remaining 2% of units, visual modulation could not be excluded with confidence (see Kral et al., 2003). The proportion of these "unclear responses" was the same in deaf and hearing animals. Additionally, subthreshold activations also were analyzed using the CSD method. Also here, no responses that could be classified as visually evoked were found.

These findings at least indicate that visual reorganization does not include the *primary* auditory cortex in deaf animals. The primary auditory cortex has the capability to reorganize to process visual inputs if the visual input is redirected to the auditory thalamus, such as may occur when the inferior colliculus is removed by aspiration (Sur et al., 1990; Roe et al., 1992; Pallas and Sur, 1993; Pallas et al., 1999; von Melchner et al., 2000; Pallas, 2001). This situation is, however, not comparable to congenital auditory deprivation, when all anatomical pathways are morphologically intact. The lemniscal auditory pathway is most likely heavily structurally patterned by molecular markers (review in Sur and Rubenstein, 2005), which include repulsive factors. These repulsive factors possibly prevent the invasions of new fibers from the nonauditory nuclei of the thalamus or from nonauditory cortical areas into the primary auditory cortex. Extensive morphological distortions are necessary to overcome these barriers. The consequence is a weaker capacity for cross-modal reorganization in the primary auditory cortex than in higher order auditory areas, which are normally bi- or polymodal.

Reduced afferent input causes the primary cortex to become hypersensitive to cochlear-implant stimulation in congenitally and neonatally deaf animals (Kral et al., 2005; Raggio and Schreiner, 1999; cf. also Kotak et al., 2005; for further mechanisms cf. Turrigiano and Nelson, 2004). A slight but significant increase in spontaneous activity has been demonstrated even in anaesthetized animals (Kral et al., 2003). These results further support the assumption that the primary auditory cortex has less ability of cross-modal reorganization than higher order cortices.

If cross-modal reorganization of the primary auditory cortex can be ruled out as a direct source of the deficits in congenitally deaf, two alternative explanations of the deficits that are typical for congenitally deaf animals are functional degeneration and functional misguided maturation.

Developmental plasticity

The development of the normal auditory system in hearing animals has been studied extensively (reviews in e.g., Payne, 1992; Cant, 1998; Sanes and Walsh, 1998), but information about the development of a naïve auditory system is sparse and the deficits resulting from the congenital deafness were unclear for a long time. Below, we will review the developmental sequence of a hearing auditory system.

Cat's middle ear is filled with a viscous, embryonic mesenchymal tissue till the end of the second week of life and the cochlea only slowly gains functionality during this time (Brugge et al., 1978). The first sound-evoked cortical responses at very high stimulus intensity can be elicited between day P3 and P8 in the cat; however, the thresholds decline under 100 dB sound pressure level (SPL) first after P10 (Konig et al., 1972; Brugge et al., 1988; Brugge, 1992). The development of hearing sensitivity (lowest unit thresholds) proceeds in different nuclei of the afferent auditory pathway with a similar time course

and reaches maturity around between P15 and P20 (auditory nerve: Kettner et al., 1985; Walsh and McGee, 1987; cochlear nucleus: Brugge et al., 1978; Brugge and O'Connor, 1984; central nucleus of the inferior colliculus: Moore and Irvine, 1979; Blatchley and Brugge, 1990; A1 field of the auditory cortex: Brugge et al., 1988; Eggermont, 1996). Interestingly, these data also correspond well with behavioral changes in hearing sensitivity of the cat (Ehret and Romand, 1981). Also the thresholds of auditory brainstem-evoked responses in the cat follow the same time course (Walsh et al., 1986). Consequently, it can be concluded that the development of sound sensitivity (in terms of neuronal thresholds) is determined by cochlear sensitivity in the cat. However, the sensitivity to low-frequency sounds develops before the sensitivity to high-frequency sounds in many vertebrates (review in Brugge, 1992). There is no evidence of units with sensitivity to stimuli of frequencies >10 kHz before P10 in the cat. Central mechanisms contribute little, if at all, to these developmental changes, and the development of functional properties in the central auditory system follows tightly the development of the cochlea.

Spontaneous activity represents a property that is difficult to evaluate, as it is strongly influenced by anesthesia. Nonetheless in anesthetized cats, the maturation of spontaneous activity was noted to reach adult values at P70 in the auditory cortex (Eggermont, 1996). This property follows the increase in synaptic densities in the visual cortex of the cat during the first 30 days (see above, Cragg, 1975). Minimum latency for tone pips is decreasing steeply in the auditory cortex of the cat, from 40–60 ms between P9–12 to 18 ms at P40, when mature values are reached (Brugge et al., 1988; Eggermont, 1996; for electrical stimulation see Kral et al., 2005). This maturational sequence is most probably related to maturation of synaptic currents, and less to myelination of geniculocortical radiation, which continues beyond this age (visual system: Tsumoto and Suda, 1982) and possibly is counterbalanced by an increase in length of this projection (Eggermont, 1996).

Studies of spectral filtering by cortical cells have shown that the proportion of broadly tuned units *increase* with age, thus causing the mean width of tuning curves to increase (Brugge et al., 1988; Eggermont, 1996; Bonham et al., 2004). Broadly tuned units are mainly found in the ventral and dorsal parts of adult A1 (Schreiner and Mendelson, 1990; Heil et al., 1992; Schreiner and Sutter, 1992). These parts of the cortex are not responsive in young animals (Bonham et al., 2004). The finding of increasing bandwidth of units in field A1 contrasts the findings of decreasing bandwidth of tuning curves in the cat inferior colliculus during the first 30–35 days post natal (Moore and Irvine, 1979). Several factors are involved in shaping cortical tuning curves. Inhibition, thalamic divergence, and type of interaction (corticocortical vs. thalamocortical) are the most important ones. Also, the range of audible frequencies increases within the first weeks of life; a factor can have biased investigations of frequency tuning in the cortex (for rats, cf. Zhang et al., 2001). However, the spatial extension of excitation at the auditory cortex from peripheral stimulation is larger in young animals than in adults, both in cats and rats (between 30 and 90 days of age in the cat stimulated electrically through a cochlear implant, Kral et al., 2005). This indicates a higher thalamocortical divergence in young animals.

The temporal properties of cortical units develop slowly postnatally. The best modulation frequency increases after birth to reach adult-like values at the age of 60 days, but the maximum best modulation frequencies were observed first at 150 days of age (Eggermont, 1991, 1996). It may be related to changes in inhibitory function after birth, which cause a suppression of the spontaneous activity after the onset response and result in a rebound response at 120–150 ms after the stimulus (Eggermont, 1992). Rebound response matures at approximately 150 days of age (see also Kral et al., 2005). This means that temporal properties are among the slowest to develop in the primary auditory field.

Owing to the fact that the auditory system undergoes a massive reorganization during development (especially in altricial animals), the ability to adapt to external influences

during development is much higher than in mature (adult) animals. The basic underlying mechanism for plasticity, at least in its first step, is the modification of synaptic efficacy by repetitive stimulation of the synapse (long-term potentiation, LTP, Bliss and Lomo, 1973) and the opposite process, long-term depression (LTD, Ito et al., 1982). For LTP, the stimulation of the synapse has to be frequent, and the pre- and postsynaptic elements have to be activated successively in a short temporal window (~10 ms, Markram et al., 1997; Zhang et al., 1998). For LTD, the stimulation has to be sparse and the coupling of presynaptic and postsynaptic activation has to be weak. In young animals, LTP and LTD can be elicited more easily than in adults (Crair and Malenka, 1995; Sermasi et al., 1999b). The time span during which LTD can be elicited more easily is longer than the corresponding period for LTP (Rittenhouse et al., 1999), indicating a period of life when the capability for synaptic depression is still larger but the LTP is already adult-like. Higher susceptibility to LTP/LTD in young animals is related to the above-mentioned changes in the composition of *N*-methyl-D-aspartate (NMDA) receptors and the exchange of NMDA receptors by AMPA receptors in the early postnatal development, and many other mechanisms further participate in this process (for review see Kaczmarek et al., 1997; Syka, 2002).

Deafness and cortical development

Functional development of the primary cortical areas (field A1) was significantly different in auditory deprived animals (congenitally deaf cats) compared with animals with normal hearing (Kral et al., 2005).

The controls in these experiments were normal hearing animals whose hair cells were acutely (at the beginning of the experiment) destroyed by intracochlear application of neomycin. The auditory nerve was stimulated electrically using a cochlear implant. In these "hearing" controls, electrical stimulation of the auditory nerve led to small-amplitude ($<100\,\mu V$) long-latency (>50 ms) responses on postnatal day 8 (before hearing thresholds have fallen under 100 dB SPL). Later in life, amplitudes increased and latencies decreased in these animals. The same stimulation activated an increasingly larger cortical area up to the age of 2–3 months (Fig. 6). Afterwards, the activated cortical area shrunk to reach the size it has in adults at 4

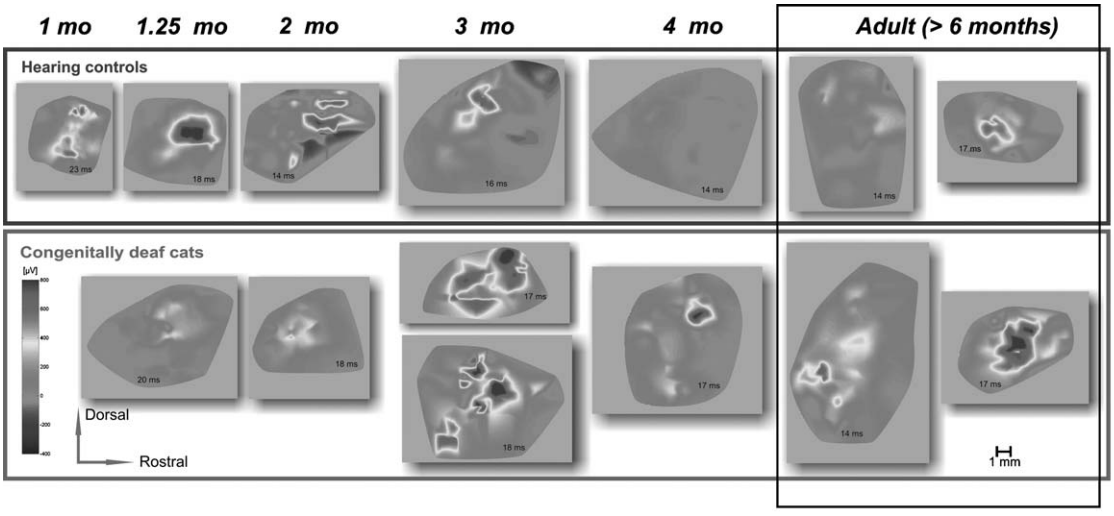

Fig. 6. Representative example of activation maps computed from maximal amplitudes of local field potentials (Pa amplitudes) in 10 hearing and 10 deaf animals at different ages. Top: hearing controls show largest activations between 1 and 2 months post natal. Afterwards, maximal amplitudes and activated areas decrease. Bottom: in congenitally deaf cats, maximal activated areas were observed at 3 months post natal (data from Kral et al., 2005). See Plate 18.6 in Colour Plate Section.

months post natal. This pattern corresponds to the one obtained with acoustical stimulation in cats (Bonham et al., 2004).

In very young deaf kitten (up to 3 months post natal), the activated areas were smaller than in their hearing counterparts. At approximately 3 months after birth, the activated region became significantly larger in congenitally deaf cats than in the hearing counterparts. From 4 months on, the activated area droped below the peak values at 3 months (Fig. 6).

The above-mentioned experiments confirm that the developmental sequence of changes in cortical activated areas is heavily modified by deafness. Preliminary data with independent component analysis of the local field potentials recorded in different cortical layers indicate that a substrate of the above differences may be a desynchronized thalamocortical and corticocortical excitation in congenitally deaf cats (Hubka et al., 2004). Additionally, a less variable pattern of sink and sources between and within neighboring columns of the field A1 was observed in deaf animals, with a particular reduction in occurrence of current sources. These findings correspond well with the above-mentioned disinhibition in the auditory cortex following auditory deprivation. Also, this pattern may indicate that an early developmental stage of cortical wiring has not been patterned by sensory stimuli and therefore could not mature properly (comp. Kalisman et al., 2005).

When local field potentials were analyzed for their morphology, additional developmental deficits were revealed in congenitally deaf cats (Kral et al., 2005); the regular developmental sequence in morphology of local field potentials evoked by electrical stimulation via a cochlear implant was delayed and modified in deaf cats (Fig. 7). Especially, the development of a mature-like wave Nb in the middle latency evoked responses was incomplete and delayed by two months in deaf animals. Wave P1 in the long-latency evoked potentials appeared early in development in a similar way as in hearing animals. However, the amplitude of this component decreased with increasing age and it nearly disappeared in adult deaf cats. Two conclusions can be drawn from the results of this study:

1. The development of the auditory cortex is sensitive to auditory experience (or its absence). Only under the influence of auditory experience an appropriate functional development of primary auditory cortex can occur.
2. The developmental sequence is altered in two ways by congenital auditory deprivation: maturation of certain properties of the auditory cortex is delayed and others show degenerative processes during development. An active shaping influence of the auditory experience can be inferred from these results.

To clarify the substrate of these changes within the auditory cortex, CSD analyses with stimulation through a cochlear implant were performed within the ROI (see above) during development (Fig. 8). The comparison revealed that in hearing controls, the gross synaptic currents increase significantly during development, reaching a peak within the second month of life. Afterwards, the maximal currents decrease. Additionally, individual currents become more and more structured in the temporal domain, indicating that the underlying individual synaptic currents shorten in duration and overlap less in time. At approximately 3 months of age, the sinks reach a fine structure that corresponds to the one in adult hearing cats stimulated through a cochlear implant. The peak in the synaptic currents occurs at the time when the synaptic densities in the visual cortex reach their maximum values (Cragg, 1975; Winfield, 1981, 1983). That does not necessarily mean that the maximum gross synaptic currents are an accurate measure of synaptic densities, but it indicates that in hearing cats the synaptic densities and the time functions of postsynaptic currents developed coherently during the second month of life and in such a way that they produce the largest gross synaptic currents. It may be assumed that at this age, the synaptic currents and their synchronization reach maturity, and that the synaptic density is the property that then determines the maximum gross synaptic current.

The development of synaptic function was different in congenitally deaf cats (Fig. 8). In these animals, the gross synaptic currents were small at 2 months of age, reached very large amplitudes at 3 months, and then decayed rapidly to give rise to

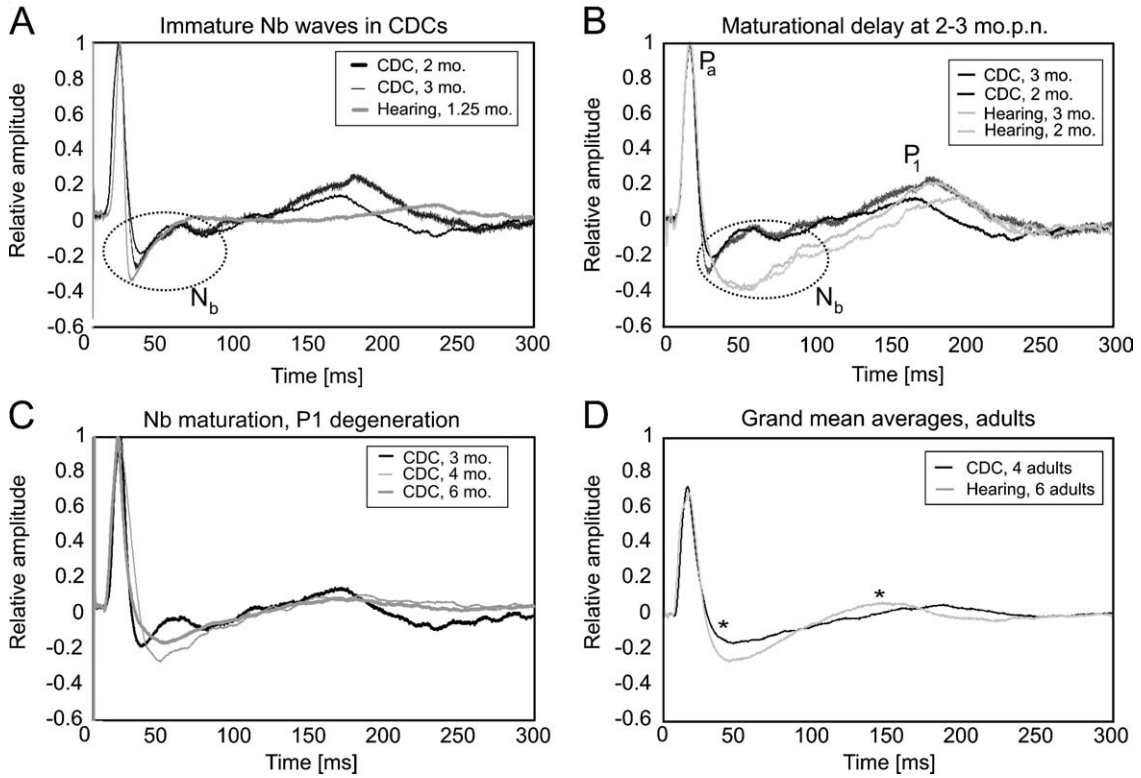

Fig. 7. Morphology of amplitude-normalized mean local field potentials in the ROI at 10 dB above threshold during development. (A) Nb waves of congenitally deaf cats at 2 and 3 months post natal compare well to the immature Nb waves obtained from hearing cats at 1.25 months post natal. (B) Age-matched deaf and hearing cats at 2–3 months post natal. Hearing controls are characterized by a mature-like broad Nb wave; the deaf cats, however, have still an immature shape of Nb wave. (C) With increasing age, the Nb wave develops in deaf cats, and the P1 wave demonstrates a degeneration with a decreasing and smeared relative amplitude. (D) Sample-to-sample comparison of grand mean averages computed from four adult deaf cats and six adult hearing controls. Deaf cats have significantly smaller Nb wave and a smaller P1 wave (Wilcoxon–Mann–Whitney test, $\alpha = 5\%$) (data from Kral et al., 2005).

patterns described in adult cats (see above). We interpret the synaptic currents to still be immature at 3 months of age, corresponding to a developmental delay. At that age, the synaptic densities are possibly still increasing in the auditory cortex, as at the corresponding age in naïve visual cortex (in contrast to that of sighted animals) the synaptogenesis is still in progress and the eventually reached peak synaptic density is amplified (Winfield, 1981, 1983). Immature synaptic densities and the abnormally large synaptic current may combine at this age to give rise to the large peak in both gross synaptic currents and activated cortical areas. Further morphological studies are necessary to verify this hypothesis and to determine the time course of synaptic development in the auditory cortex.

Is the "deaf" A1 functionally decoupled from higher order auditory cortical areas?

The deficits found in a naïve cortical microcircuitry may have functional significance with two important implications:

1. A desynchronization of activity between cortical layers, particularly a delay in activation of supragranular layers, disables the proper function of the cortical intrinsic microcircuitry in field A1 of deaf cats. A synchronous activation of the pyramidal cells of layer V at different portions of their dendritic tree (at the level of supragranular layers) switches the cell into a different processing mode (e.g.,

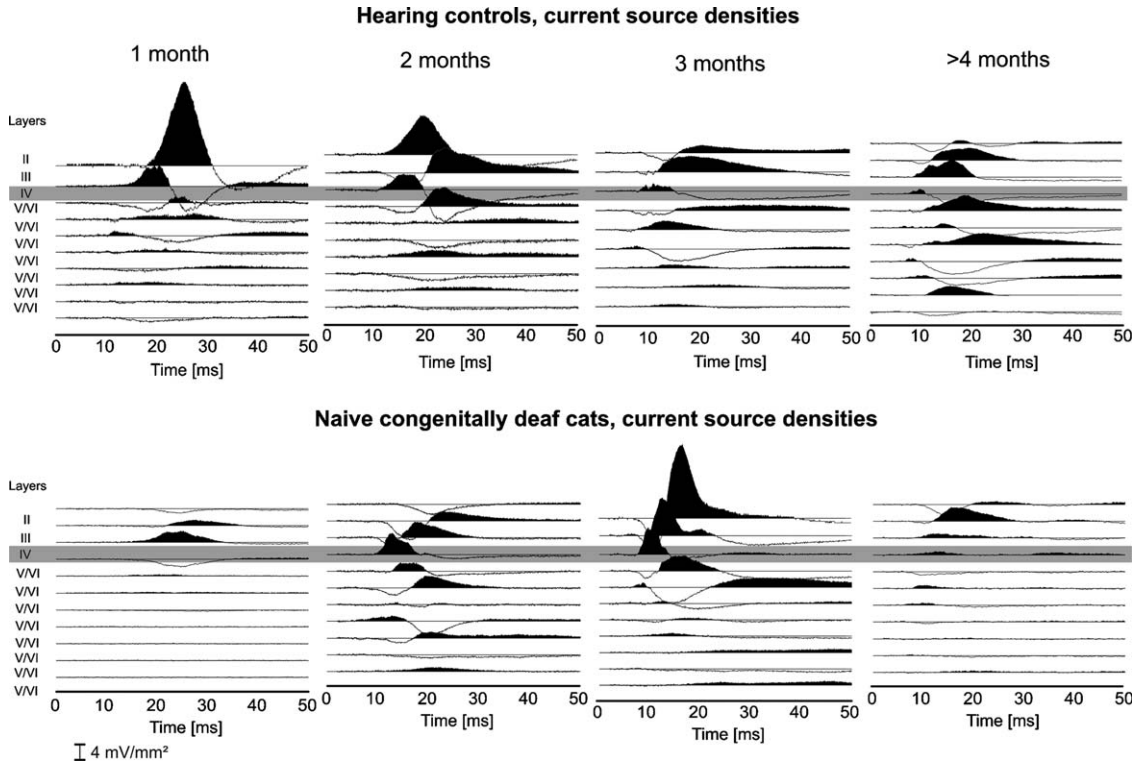

Fig. 8. CSD signals obtained during development in hearing controls and deaf cats. Largest signals obtained in hearing controls between the first and the second month post natal; in deaf cats, this peak is delayed to the age of 3 months post natal. Subsequently, the deficits in CSD profiles as described in adult deaf cats develop (reproduced with permission from Kral et al., 2005). For details see text.

Larkum et al., 1999; Llinas et al., 2002), which is important for the proper relay of information from the cortex to its targets (cortical and subcortical). Therefore, the naïve auditory cortex might not properly activate the "output cells" in the infragranular layers of the primary auditory cortex.

2. The observed reduction of activity in infragranular layers further supports the mplications above and additionally indicates that corticofugal projections (e.g., corticothalamic feedback) do not function properly. It is therefore probable that the function of thalamocorticothalamic and corticocortical loops is compromised in deafness. Reductions in infragranular layer activation also points to a reduced activity in descending cortical projections, which target these layers and which are thought to convey a cognitive top-down modulation of activity (Raizada and Grossberg, 2003), further indicating that the primary auditory cortex is decoupled from other cortical fields in congenital deafness.

Hearing after congenital deafness: chronic stimulation with cochlear implants

To what extent are all these deficits caused by the absence of auditory input, and to what extent the findings represent an intrinsic difference in the molecular or structural constitution between hearing and congenitally deaf cats? The differences in genetic makeup of congenitally deaf cats (CDCs) might show up also at other structures, in addition to the cochlea. However, attempts to reveal such differences were unsuccessful so far: Studies of the cerebellum (West and Harrison, 1973) and the nucleus of the trigeminal nerve (Saada et al., 1996)

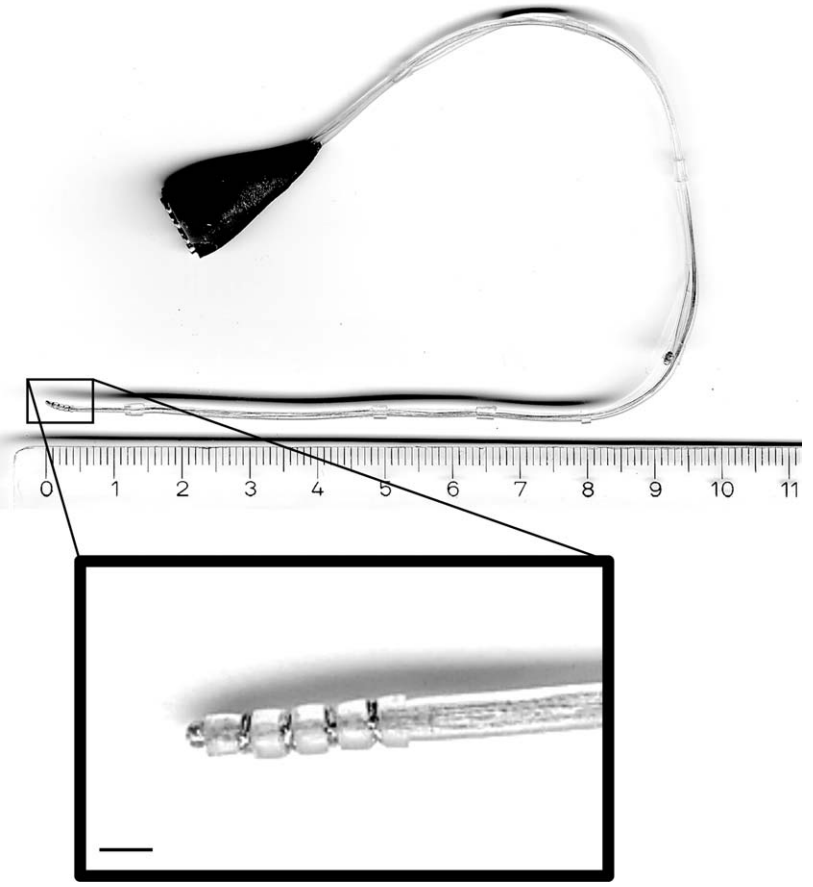

Fig. 9. A cochlear implant developed for chronic electrical stimulation in congenitally deaf cat (after Behrendt, 1999). Scale in centimeters; bar in the inset = 1 mm.

have not demonstrated any difference between congenitally deaf cats and hearing controls.

It would be a strong argument for the hypothesis that the abnormalities are caused by deprivation of input to the auditory system if the known signs of functional deficits in congenitally deaf cats were reversed by auditory experience. For that purpose, the capacity for plastic reorganization during development has been investigated using cochlear-implanted animals to activate the auditory system in congenitally deaf cats.

> The auditory nerve was stimulated electrically in congenitally deaf cats using cochlear implants inserted through the round window (Fig. 9, cf. Behrendt, 1999). The implant was fed transcutaneously in the interscapular line and covered by a tissue jacket with a backpack. After a healing phase of 3–7 days post implantation, the animals were first tested with a sinusoidal stimulus applied through the implant. The "hearing thresholds" for electrical stimulation in these animals were determined by observing the pinna orientation reflexes visually during presentation of these electrical stimuli. Thresholds of pinna orientation reflexes correspond to hearing thresholds in hearing cats (Ehret, 1985). Congenitally deaf cats have preserved pinna orientation reflexes (Klinke et al., 1999; Kral et al., 2002). The pinna orientation thresholds were well reproducible in each animal and the threshold increased with 6 dB/octave with increasing stimulus frequency, comparably to thresholds of auditory nerve fibers (Hartmann

and Klinke, 1990). Using the assumption that the threshold of these reflexes corresponds to the perceptual thresholds also in these animals, the reflex thresholds were considered as valid measures of the hearing thresholds.

After determining the threshold of cochlear electrical stimulation, the animals were equipped with a signal processor using a compressed analog coding strategy delivered in a monopolar configuration to the most apical electrode of the implant (Klinke et al., 1999). The signal processors were adjusted to the individual threshold curve to reach thresholds at an acoustical stimulation level of 65 dB SPL at each frequency from 125 Hz to 8 kHz. The maximum electrical current was limited to 10 dB above threshold. The stimulation was applied without interruption (except the short times of battery control and impedance tests of the electrodes) for 1.0–5.5 months. During the stimulation period, the animals were conditioned to simple acoustic stimuli through their cochlear implants and they learned to react to an acoustic stimulus within 10–18 training sessions (i.e., in a two alternative forced-choice paradigm, the success rate exceeded 60%). The animals lived in the standard animal-house environment during the chronic stimulation. They heard, via electrical stimulation through the portable signal processor, all sounds above 65 dB SPL within the range of 125 Hz–8 kHz. These sounds included environmental sounds during handling of the animals, their own vocalizations, vocalizations of other cats from the colony, and sounds produced during play. In this respect, the animals with cochlear implants lived in a more or less "normal" acoustic environment of a standard animal-house condition.

After 1.0−5.5 months of auditory experience, auditory cortices of these animals were investigated in final experiments. With the strategy described above, the auditory cortex was mapped using surface-recorded local field potentials. In general, the lowest cortical thresholds (in naive cats significantly lower than in their normal hearing counterparts acutely deafened and stimulated electrically) were not significantly affected by chronic electrical stimulation (Kral et al., 2002).

The functional organization of the auditory cortex was significantly changed by hearing experience. The most prominent difference between the stimulated CDCs and the unstimulated CDCs was the larger activated cortical area: with increasing stimulation duration, the area responding to the stimulation (biphasic pulse 200 μs/phase, monopolar configuration) grew up to a factor of 5 (Fig. 10). This finding agrees with the findings of enlarged representation of the stimulus in hearing animals after conditioning or pairing the stimulus with electrical stimulation of basal nucleus (e.g., Kilgard and Merzenich, 1998). The expansion of the activated area seems to be a meaningful reorganization when the stimulation is done with a single-channel electrical stimulation because it provides more neural tissue to process the incoming activity. By that, more computational power for processing of the stimuli is guaranteed.

The increase in the activated areas was a slow process, taking many weeks to months. Therefore, this process has to involve extensive morphological reorganizations. The process was not confined to the auditory cortex contralateral to the implanted ear, but the representation of the stimulus at the ipsilateral cortex also expanded, although to a lesser degree than that at the contralateral cortex (Kral et al., 2002). It is not known if these changes in cortical representation are caused by subcortical reorganizations, or if both cortical reorganizations are solely of cortical origin. The findings on corticofugal plasticity in hearing animals (e.g., Ma and Suga, 2003; Suga and Ma, 2003) suggest that the reorganization that occurs after activation of the auditory nervous system in naïve animals is primarily of cortical origin, with subcortical reorganization following afterwards.

Extension of the cortical representations does not mean that processing of auditory stimuli has changed. Therefore, within the most activated cortical area, single- and multiunit activity was further analyzed. Here, a more complex pattern of responses showed up in trained animals: the cortical units showed a higher diversity in their response patterns. Poststimulus time histograms revealed several different types of unit responses (Klinke et al., 1999). The occurrence of

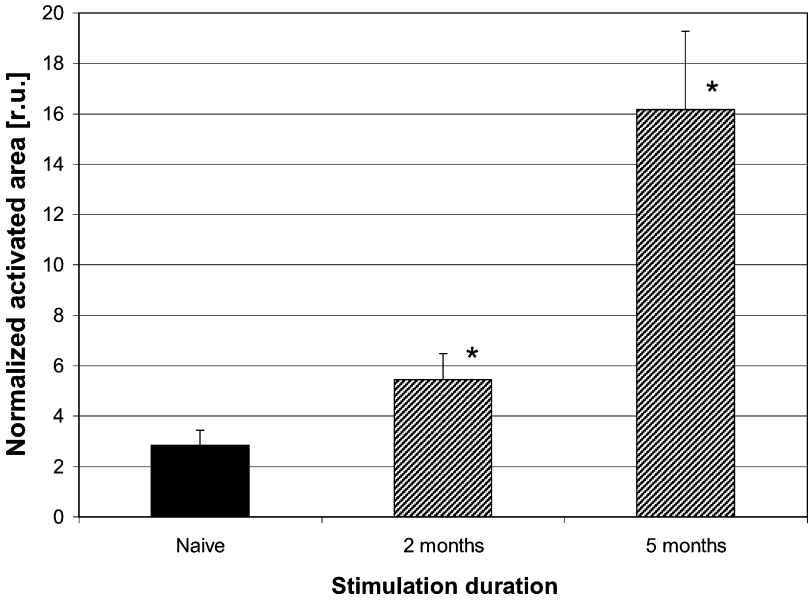

Fig. 10. Increase in the activated area with increasing duration of chronic electrical stimulation (four, two and two animals, respectively). Activated areas were normalized to body weight (details in Kral et al., 2002), although the same effect was observed also without normalization. Significant differences between naïve animals and animals stimulated 2 months, and also between animals stimulated 2 months and 5 months (Wilcoxon-Mann-Whitney, $\alpha = 5\%$; reprinted with permission from Kral et al., 2002).

long-latency responses increased after chronic electrical stimulation, indicating that activity within the trained auditory cortex can persist for a longer time and is more similar to activity evoked by acoustic stimulation in hearing animals (compare Eggermont, 1992). Since this increase in occurrence of long-latency responses was not connected with a significant decrease in cortical thresholds, we can assume that the observed signs of cortical reorganization are not the consequence of a general increase in cortical sensitivity. Long-latency responses in hearing animals have been attributed to a rebound of inhibition (e.g., Eggermont, 1992), and the observed increase of cells with these responses indicate a more complex excitatory–inhibitory interaction after training. Different units not only began to respond differently to the same stimulus, but the responses also became more complex (Fig. 11, cf. Kral et al., 2001). These findings indicate that the naïve cortex develops feature-detection abilities after training, as different units respond differently to the same stimulus, and different stimuli are responded differently by the same unit.

In addition to these changes, the processing of the incoming information within the intrinsic cortical neuronal networks changed after chronic electrical stimulation. With increasing stimulation duration, the CSD signals increased in amplitude (Fig. 12). This was true for both mean sink amplitudes and mean sink latencies. That means that chronic electrical stimulation (auditory experience) significantly increased the synchronized synaptic activity in the primary auditory cortex. These changes reached a plateau after approximately 3 months of stimulation. It is interesting that the synchronized synaptic activity saturated at a higher level than in hearing controls. This not only demonstrates that the cerebral cortex in naive animals has a high capacity for plastic reorganization, but also shows that chronically stimulated animals have specialized for processing of electrical stimuli. The other interesting finding relates to the structure of the CSD profiles: after 3 months of stimulation they also showed a profile that corresponded well to the one from hearing controls (Fig. 12). The latencies of the earliest sinks approached the one described in hearing controls.

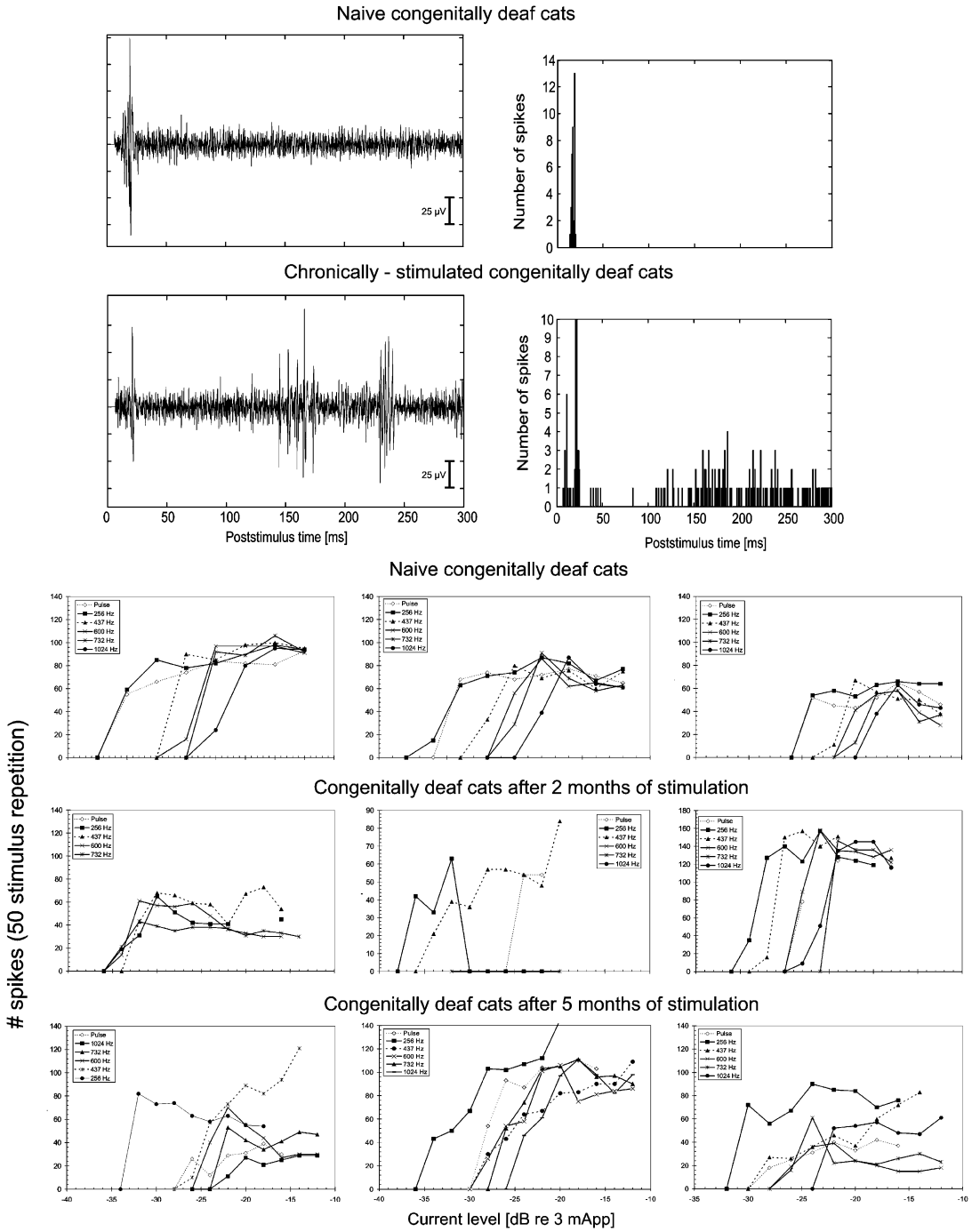

Fig. 11. Single trace of a multi-unit response to electrical stimulation (left) and the corresponding post-stimulus time histogram (right) in field A1 of a naïve and a chronically-stimulate CDC. Below: Rate-intensity functions of single- and multiunits from ROI in naïve and chronically stimulated congenitally deaf cats. Top: in naïve animals, the variability of the rate-intensity functions is rather small, dynamic range is <6 dB, and thresholds increases by approximately 6 dB with doubling of the frequency of the stimulus. Middle: after 2 months of stimulation, rate-intensity functions changed; the dynamic range increases (middle), and units with selective to certain characteristics of the stimulus appear; however, there are also units comparable with those from naïve animals (right). Bottom: after 5 months of stimulation, units appear that respond differentially to different characteristics of stimuli, and the dynamic range of responses increases (data from Klinke et al., 1999 and Kral et al., 2001). Conditioned stimuli: 437 Hz and 732 Hz.

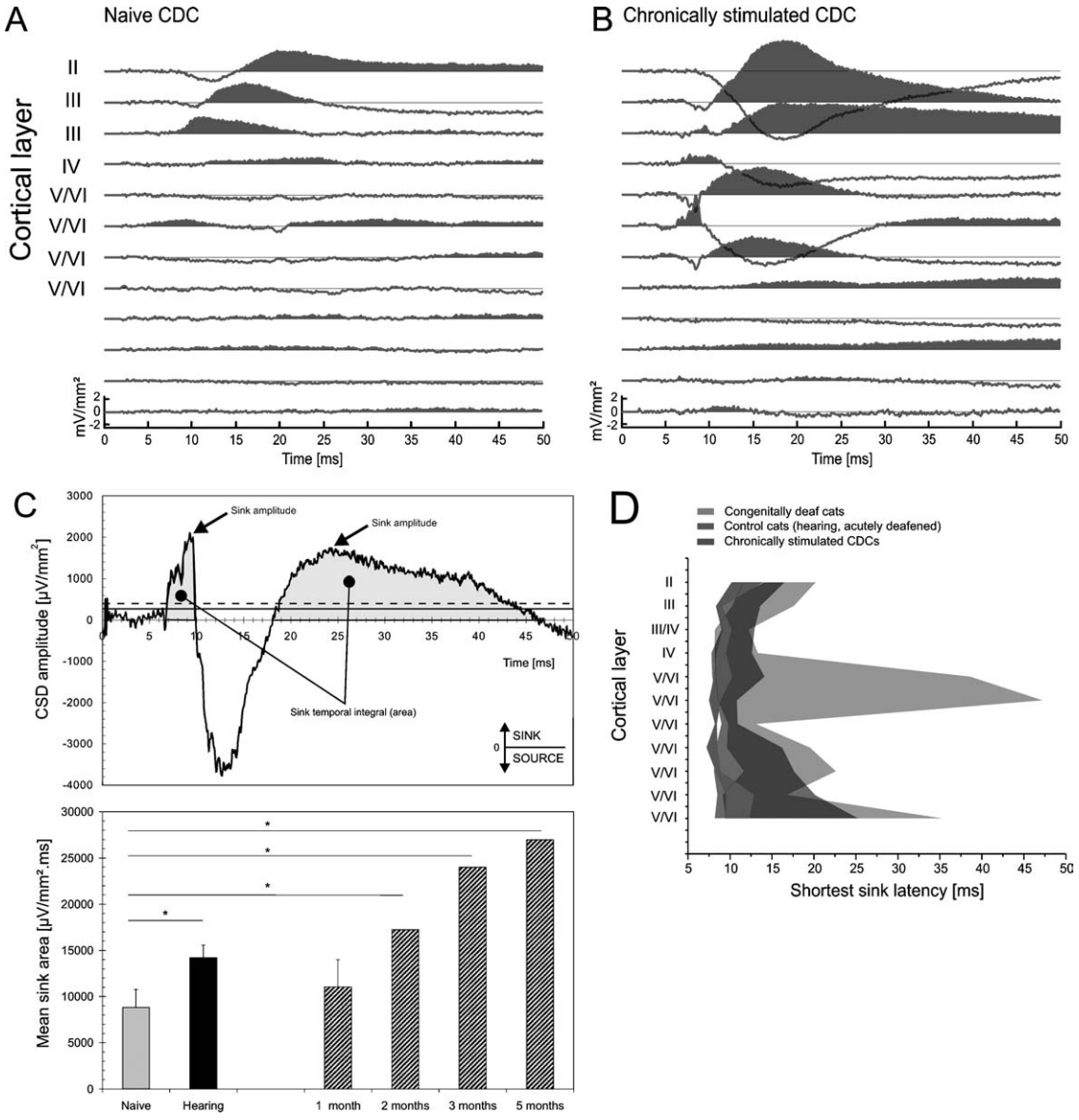

Fig. 12. CSD signals normalize after chronic electrical stimulation through cochlear implants (sinks are filled). Representative comparison between age-matched naïve congenitally deaf cat (A) and chronically stimulated deaf cat after 5 months of electrical stimulation (B). More activity was found in deep cortical layers of chronically stimulated cats. (C) Quantitative analysis of the above data. Mean sink temporal integrals increase with increasing duration of chronic electrical stimulation (mean data from ROI, 1 months stimulation: two animals; 2–5 months of stimulation: one animal; all animals shown here were implanted at 3 months after birth; Wilcoxon–Mann–Whitney test at $\alpha = 5\%$). (D) Shortest sink latencies decreased after chronic electrical stimulation and became more comparable to hearing controls. See Plate 18.12 in Colour Plate Section.

These findings are relevant to normal listening situations because synchronized activation of cortical layers are important for the normal activation of pyramidal cells in deep cortical layers (Larkum et al., 1999; Llinas et al., 2002). This can assure that the output activity in the auditory cortex is transferred not only to subcortical nuclei, but also to the ipsilateral and contralateral auditory cortex.

In addition, only an appropriately activated neuron in the deep cortical layers can receive and handle the top-down modulation from higher order auditory cortex targeting these cortical layers (review in Raizada and Grossberg, 2003). The decoupling of primary from higher order cortical areas, assumed in naïve animals, was overcome by early hearing experience.

Sensitive periods

When the above-described effects were related to the age at implantation, it was shown that the earlier the implantation took place, the more extensive were the reorganizations in field A1 of the auditory cortex that could be achieved (Kral et al., 2001, 2002) and the expansions of the activated areas were largest in the earliest implanted animals. The age effect was even more consistent in the cortex ipsilateral to the ear that was chronically stimulated. In animals that were implanted as adults (within the sixth month after birth), smaller expansions were found at both the ipsilateral and contralateral cortex when compared to young implanted animals. The developmental plasticity of the auditory cortex thus showed a sensitive period from the second to the sixth month of life in cats.

The largest reorganizations occurred at the implantation ages when the largest cortical representations occurred in naïve CDCs. This is taken as a sign of the importance of this phenomenon for the recovery after deprivation. Nonetheless, large changes could also be achieved after the cortical representations in naïve animals have shrunken (cf. Kral et al., 2002, 2005), which demonstrates that the sensitive period for recovery (effects of chronic electrostimulation) is longer than the sensitive period in development (age span when cortical representations are large). Similar findings have been presented for the visual system (recent review in Lewis and Maurer, 2005).

The sensitive period for recovery in congenitally deaf cats can be further demonstrated with the morphology of the local field potentials (evoked potentials). The latencies of the Pa wave of the field potential normally decrease with increasing stimulation duration (Fig. 13, Kral et al., 2002), but this decrease is statistically significant only after stimulation for more than 2 months in congenitally deaf cats. However, even after 5 months of stimulation, no decrease in latency of Pa occurred in animals that were implanted after the fifth month of age. Morphology of the local field potentials not only in the long-latency but also in the middle-latency range, differed between early- and late-implanted animals. The bases for these differences are changes in the spatiotemporal relation of current sinks and sources within the auditory cortex.

Growth factors play an important role in cortical plasticity. Studies of monocular deprivation have shown that infusion of brain growth factors into the cortex moves the critical period to earlier ages (Huang et al., 1999). Brain-derived neurotrophic factor (BDNF) increases the rate of the development of inhibition (review in Berardi et al., 2000). Neurotrophic factors affect the development of those synapses that are active, more than those that are inactive (Boulanger and Poo, 1999; Zhang and Poo, 2001; Nagappan and Lu, 2005). Activity can also regulate the amount of neurotrophic substances produced by neurons and the number of receptors for neurotrophins (Zafra et al., 1992; Meyer-Franke et al., 1998). These substances have a trophic effect on, e.g., growth of dendrites (McAllister et al., 1996; Horch, 2004; Dijkhuizen and Ghosh, 2005). This differential expression of neurotrophic factors during development could contribute to the creation of sensitive periods (Sermasi et al., 1999a; Lein et al., 2000), although some neurotrophins do not change their expression during development (e.g., Ichisaka et al., 2003).

The end of the sensitive period in congenital auditory deprivation coincides approximately with the onset of puberty (~6 months in cats). This of course does not mean that the auditory cortex in the adult brain lacks plasticity, but certain factors limit the extent of expression of neural plasticity in adults. Early in development, sensory experience can affect the development of the overall synaptic organization, which then leads to more efficient and durable learning than in the adult. While plasticity can be induced by "passive" listening during development (Zhang et al., 2001, 2002), a

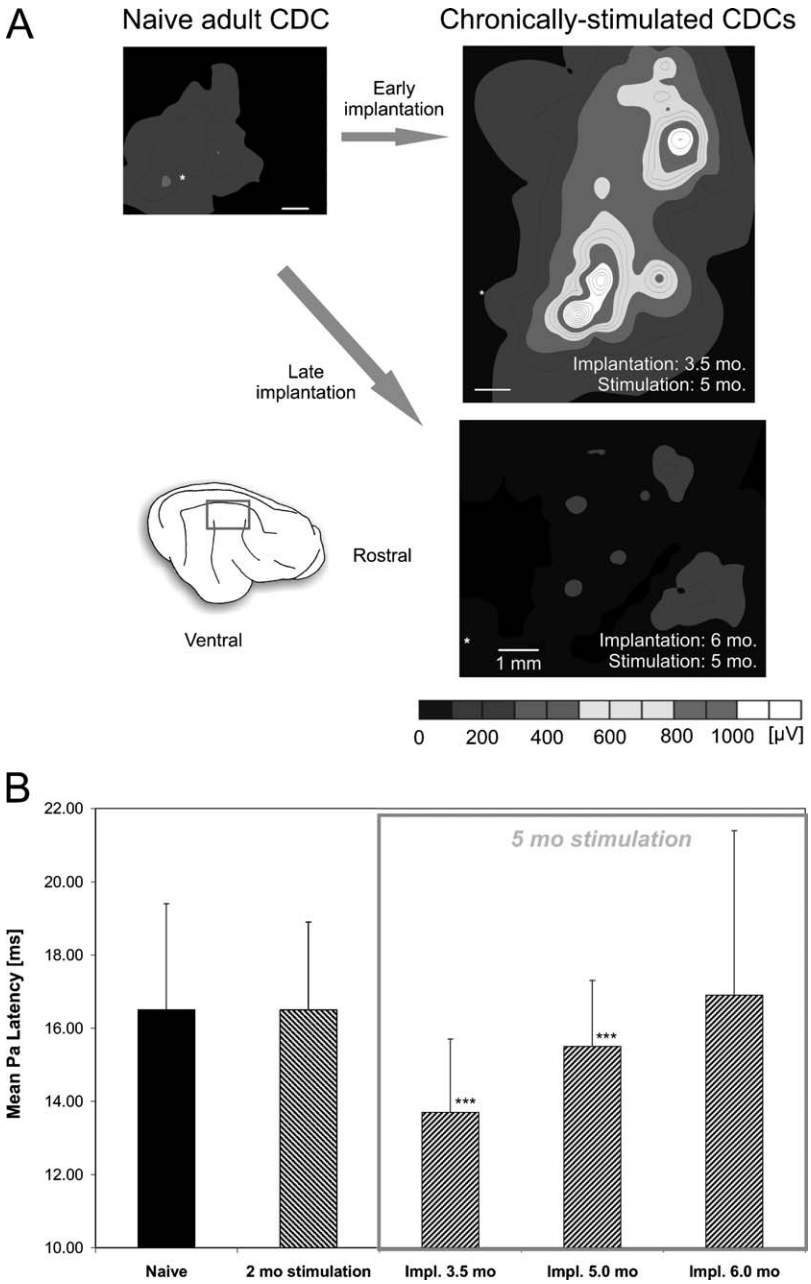

Fig. 13. The capacity for plastic reorganization with cochlear implant stimulation decreases with increasing age. (A) Massive (but slow) expansions of the cortical activated areas, as demonstrated for early implanted animals in Fig. 10, become smaller with increasing implantation age (asterisk marks the dorsal end of the posterior ectosylvian sulcus; Kral et al., 2001, 2002). (B) The sensitive period can also be demonstrated in latencies of Pa waves, that become significantly smaller after 5 months of stimulation at early implantation (age 3.5 months post natal), but this decrease was smaller after implantation age 5 months post natal and was no longer discernible with implantation in adult age (6 months post natal Wilcoxon-Mann-Whitney test, $\alpha = 0.4\%$; reprinted with permission from Kral et al., 2006). See Plate 18.13 in Colour Plate Section.

similar extent of plasticity in adults can only be achieved by pairing of stimuli with some instruction factor like electrical activation of nucleus basalis or active conditioning (Bakin and Weinberger, 1996; Kilgard and Merzenich, 2002; Bao et al., 2003). Finally, it must be taken into account that the naive adult auditory cortex might be differently reorganizing than the ''hearing'' adult cortex (in normal hearing animals) under comparable stimulation condition. After certain developmental stages have been reached in absence of auditory experience, the starting point of cortical organization will differ from the normal-hearing counterparts.

Studies of the somatosensory system have revealed an important cause of difference between early and adult plasticity. The overall number of synapses remains relatively constant in the adult barrel cortex, despite the extensive plasticity and the formation of new synaptic contacts (Trachtenberg et al., 2002). This indicates that the number of synapses, at least in the primary sensory cortex of adult animals, is relatively stable over time (for further evidence in the visual cortex, see O'Kusky and Colonnier, 1982a, b) and represents one important limiting factor for expression of adult plasticity. During development, synaptic densities change dramatically under the influence of experience (see above), so that possibly much more extensive wiring changes result within a short time. We still did not reach full understanding of the mechanism of these processes. All expressions of plasticity that have been observed at the level of synapses and receptors took place within minutes to hours, but the plasticity demonstrated in the above experiments took place in course of months.

Clinical relevance

The topics discussed in this text are of cardinal relevance in clinical practice. Diagnosis of congenital deafness is hampered by the fact that the human cochlea becomes functional already during the intrauterine life (Granier-Deferre et al., 1985), but the diagnosis of hearing loss is possible only after birth. This is why clinicians differentiate only between prelingual (before language has started being acquired) and postlingual deafness or hearing loss. The incidence of congenital hearing loss is about one per thousand. Hearing screenings have been introduced in several countries to detect hearing disabilities early (e.g., O'Donoghue, 1996, 1999; O'Donoghue et al. 1998).

There are now strong indications that the reorganizations of the auditory nervous system discussed in this chapter takes place also in cochlear-implanted prelingually deaf children. It has been known for a long time that cochlear implantation in prelingually deaf adults does not lead to ''open-set'' speech understanding (Busby et al., 1992, 1993; Dawson et al., 1992; Tyler and Lowder, 1992; Gantz et al., 1993, 1994;), and it is consequently recommend that cochlear implantation is performed before the age of 5 years (Fryauf-Bertschy et al., 1997; Waltzman and Cohen, 1998; Schauwers et al., 2004). These recommendations were further supported by electrophysiological investigations. Children that were prelingually deaf and received a cochlear implant before their teen ages showed a delay in the normal development of the morphology of cortical evoked potentials (Ponton et al., 1996a, b; Eggermont et al., 1997; for further developmental data in cochlear-implanted children, also cf. Gordon et al., 2002, 2005). The development of normal latencies of cortical evoked potentials was delayed approximately by the same amount of time as the duration of deafness. After stimulation using a cochlear implant, the latencies of the evoked potentials matured, yet the original delay in development of latencies remained as if the children were developmentally delayed by the duration of their deafness. That led the authors to hypothesize that the latency of P1 is reduced during development to an extension that corresponds to the duration of hearing experience (time in sound). Nonetheless, these authors did not study children implanted under 4 years of age. Once children implanted before their fourth year of age were evaluated in the same way as the children implanted later, it was found that the early-implanted children caught up with their maturational delays in P1 latency within few months after implantation (Sharma et al., 2002a, b, c, 2005). Consequently,

there is a sensitive period in the development of auditory evoked potentials, which corresponds to the sensitive period in speech comprehension (Fryauf-Bertschy et al., 1997).

Development of a mature N1 wave represents another sensitive period. Prelingually deaf children implanted in their teen ages do not develop a mature N1 wave, which follows the P1 wave in individuals with hearing (Ponton and Eggermont, 2001). Children implanted in their teens also do not achieve "open-set" speech comprehension without lipreading (Busby et al., 1992, 1993; Dawson et al., 1992; Tyler and Lowder, 1992; Gantz et al., 1993, 1994). It is known that higher order auditory and nonauditory areas are recruited during speech recognition in cochlear-implanted individuals and their activation correlates with achievement of speech comprehension (Giraud et al., 2000). The N1 wave is known to be generated in higher order auditory areas (Liegeois-Chauvel et al., 1994), and thus it appears as if these areas were not properly activated in prelingually deaf children implanted late (in their teens).

Studies of prelingually deaf children allow further conclusions affecting the neurophysiological question on plasticity in the naive auditory system. There are at least two phases of plastic reorganizations in the auditory cortex. The first one is a fast and extensive one, taking place in the first few weeks after cochlear implantation. The P1 latencies matured fast in the first short phase of plasticity in implanted children (Sharma et al., 2005). This phase was also found in children who were implanted late in life (the first, fast decay of P1 latency during the first few weeks after implant activation did not show a sensitive period). The second phase of decrease in P1 latency, which took place later (during the months after implantation), was much slower and less extensive, but showed a sensitive period. Late-implanted children did show this phase only in a very rudimentary way.

Conclusions

The development of the auditory system depends critically on auditory experience. In absence of hearing, the primary auditory cortex remains capable of responding to auditory stimuli, but the functionality of the auditory cortex is massively affected by the deprivation. In this respect, the naive auditory cortex represents a significantly different starting point for plastic cortical reorganizations compared to cortex in animals with hearing (acoustically-competent).

Studies of neonatally deaf animals and studies of congenitally (or prelingually) deaf children indicate that the changes in the function of the auditory cortices that occur after restoration of hearing via cochlear implants can be differentiated into three phases:

1. The first phase spans the first days and weeks after implantation in humans. This very fast reorganization process (e.g., the fast decrease of P1 latency) does not have a specific sensitive period. The changes are most likely related to restoration of inhibitory function in the cortex and restoration of homeostatic regulation of neuronal excitability, increasing the synchronization of evoked activity. It may be connected with a fast reduction of the large (immature) gross synaptic currents and large activated areas found in young congenitally deaf animals.
2. The second phase is a slower reorganization, taking place within weeks to months after implantation. These changes constitute a sensitive period in humans and animals. The corresponding reorganization most probably includes an increase in cortical representation of the stimulated cortical region, restoration of the functionality of the cortical intrinsic microcircuitry, changes in the latencies of field potentials, and CSD signals and reappearance of the long-latency responses. It is in this phase that the primary areas most probably reorganize and sharpen their feature-detection abilities.
3. The third phase is the slowest, being a consequence of the restoration of the functionality of the primary cortical areas. It involves recruitment of higher order auditory cortices by the stimulus (e.g., Giraud et al., 2001a, b c; Giraud and Truy, 2002) and involves

formation of descending projections from higher order areas to the primary areas. It is probably connected with the appearance of N1 and later waves of evoked potentials. This phase initially overlaps with phase 2.

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