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## Unimodal and cross-modal plasticity in the 'deaf' auditory cortex

**Abstract**

Congenital auditory deprivation leads to deficits in the auditory cortex. The present review focuses on central aspects of auditory deprivation: development, plasticity, corticocortical interactions, and cross-modal reorganization. We compile imaging data from human subjects, electroencephalographic data from cochlear implanted children, and animal research on congenital deafness. Behavioral, electroencephalographic, and imaging data in humans correspond well to behavioral and neurophysiological data obtained from congenitally deaf cats. The available data indicate that auditory deprivation leads to 'decoupling' of the primary auditory cortex from cognitive modulation of higher-order auditory areas. Higher-order auditory areas undergo a strong cross-modal reorganization and take-over new functions. Due to these and other deficits of intrinsic microcircuitry, the cortical column can not integrate bottom-up and top-down influences in deaf auditory cortex. In the ultimate consequence perceptual learning is compromised, resulting in sensitive periods.

**Sumario**

La privación auditiva congénita conduce deficiencias en la corteza auditiva. La presente revisión se concentra en aspectos centrales de la privación auditiva: desarrollo, plasticidad, interacciones cortico-corticales y reorganización modal cruzada. Compilamos datos de imágenes de sujetos humanos, datos electroencefalográficos de niños con implante coclear, y de investigación en animales sobre sordera congénita. Los datos conductuales, electroencefalográficos y de imágenes en humanos correlacionan bien con los datos conductuales y neurofisiológicos obtenidos de gatos sordos congénitos. La información disponible indica que la privación auditiva conduce a un desacople de la corteza auditiva primaria con respecto a la modulación cognitiva de las áreas auditivas de orden superior. Estas sufren una reorganización modal cruzada fuerte y toman posesión de nuevas funciones. Debido a éstas y a nuevas deficiencias de los microcircuitos intrínsecos, la columna cortical no puede integrar las influencias ascendentes y descendentes en la corteza auditiva sorda. Como una consecuencia final, se pone en peligro el aprendizaje perceptual, y por consiguiente, los períodos sensibles.

Cochlear implants serve to replace a non-functional inner ear by direct electrical stimulation of the auditory nerve fibers. Yet, there are substantial differences in the acoustically- and electrically-evoked response patterns in the auditory nerve:

- The high spontaneous activity normally found in auditory nerve fibers is absent in deaf animals. Spontaneous activity is the consequence of spontaneous release of glutamate at the synapse between the hair cell and the primary afferent. Among other important factors it also decreases the coupling between the stimulus and the response, which allows the modulation of firing rate over a wider range of stimulus intensities (larger 'dynamic range'). That allows coding of stimulus intensity by firing rate. The consequence of the absence of spontaneous activity is an increase in the coupling between stimulus and response (a 'hypersynchronization' of the responses to the stimulus, review in Hartmann & Kral, 2004), and by that a reduction of the dynamic range. The hypersynchronization of the electrically-evoked activity may have a boosting effect on central plasticity, as action potentials are more likely to arrive synchronously on central neurons. Synchronous action potentials increase the likelihood of plastic changes at activated synapses (see below).
- The spread of activation in the auditory nerve is much larger with electrical stimulation than with acoustical stimulation. Even the most focused stimulation strategies (e.g. with the tripolar electrode configuration; Kral et al, 1998) do not come

close to the acoustical stimulation and, in addition, are not favorable in cases of patchy degeneration of the auditory nerve. On the other hand, more focused stimulation along with many advantages has also certain unfavorable effects on the dynamic range of the electric hearing.

- Simultaneous activation of several electrodes can lead to unwanted current flows between the active electrodes. Therefore, interleaved stimulation is used, which further biases the temporal excitation pattern when compared to natural acoustically-evoked activity.

For these and other reasons, following cochlear implantation the auditory system has to learn to process the new auditory input. Plasticity refers to the ability of the neurons and neuronal networks to change their function in consequence of their previous activity. The expression of neuronal plasticity increases up the way from the cochlea to the cortex (e.g. Kamke et al, 2003). Thus, the auditory cortex and the thalamus have a higher plasticity than centrifugal structures (e.g. inferior colliculus or cochlear nucleus). Furthermore, higher-order auditory cortex has a higher capacity for plastic reorganization than primary auditory areas (for review, compare Kral & Tillein 2006). Mechanisms of neuronal plasticity have been the focus of interest in research for many decades. Plasticity is based in part on changes in synaptic function (synaptic plasticity), on change in synchronization in the neuronal networks, and on change in interneuronal connection patterns within neuronal networks.

The brain has to build up its complex architecture during development. Two different developmental phases of cerebral cortex can be differentiated: the first one is the early phase, when cortical development is independent from external (sensory) inputs (and motor outputs). This phase terminates when the thalamic afferents reach the cerebral cortex. Thereafter the late phase of development takes over, during which sensory inputs can shape the developmental process. The penetration of thalamic afferents into the cerebral cortex takes place 3.5 days after birth in rats, a few days ( $\sim 5$ ) before birth in cats, and in the middle of the intrauterine life in humans (for details, see Clancy et al, 2001). In what follows, 'development' will refer only to the late developmental phase after the thalamic afferents have penetrated into the cerebral cortex; the early phase will not be discussed in the present text. Developmental plasticity refers to changes of neuronal function evoked by sensory stimulation during development.

Perceptions related to hearing are here referred to as *Auditory events* ('objects'). They are in most cases caused by or related to sound events. *Sound (acoustic) events* ('objects') can thus be characterized either by their source or generation mechanism (like a 'miaow' as a vocalization of a cat) or by acoustic features (the physical properties of the sound). The most simple acoustic features are frequency composition (sound spectrum), sound intensity and sound duration. A certain subset of these features is characteristic for an auditory object. Acoustic features can be used as dimensions defining a *feature space*. Topological organization of features within a neuronal network results in a *feature map*. Auditory objects result of a two step process: first of discrimination of acoustic features (and their representation within the auditory system); and second of their subsequent synthesis into a unique auditory category. Auditory objects are not simple transformations of acoustic objects; auditory objects are representations based on biological relevance of the physical stimuli. There is no isomorphy between acoustic and auditory objects: small differences in acoustic features can differentiate two different auditory objects, whereas even large feature differences can be irrelevant for the organism and, despite the acoustic differences, the sounds may be categorized to the same auditory object.

The primary auditory cortex shows sensitivity to elementary features of sounds. Some of these features are also topologically arranged. A classical example is the arrangement to the stimulus frequency to which individual cortical neurons are most sensitive: the 'best' frequency is topologically organized at the primary auditory cortex, forming a tonotopic map (fMRI, humans: Formisano et al, 2003; single cell recording, humans: Howard et al, 1996; single cell recording, cat auditory cortex: Reale & Imig, 1980; original description, electrophysiology, cat: Woolsey & Walzl, 1942).

Some feature sensitivity in the primary sensory cortex is inborn. In the visual system ocular dominance and orientation selectivity can be demonstrated in field V1 before eye opening (Crair et al, 1998; Horton & Hocking, 1996). Accordingly, visual pattern classification can be demonstrated in newborn babies (Easterbrook et al, 1999). A child under the age of  $\sim 12$  months (in contrast to adults) has the capacity to differentiate individual faces of monkeys (demonstrating a high level of feature analysis; Pascalis et al, 2005). However, there is also the evidence that certain feature detectors need experience to develop: e.g.

direction selectivity in field V1 requires sensory input for development (ferret: Li et al, 2006).

Accordingly, very small children (up to  $\sim 6$  months post-natally) have the capacity to differentiate all sound contrasts of all languages, demonstrating a high level of feature analysis (Werker & Tees, 1984b, 1983; for review, compare Goldin-Meadow, 2003). However, for language understanding another property is essential: the development of phonemic categories. Individual instances of a phoneme, even if spoken by the same speaker, differ in their acoustic features (e.g. frequency of individual formants, their onset timing, their duration, etc.). To be able to abstract from their individual (varying) acoustic features, the brain has to learn to focus only on those features that are *distinctive*, i.e. which are the same for each instance of the same phoneme and which, at the same time, differentiate that phoneme from all other phonemes in the given language (Flanagan & Rabiner 1973). Examples of such features are mutual relations between the frequency of the formants, their shifts with time (glides), noisiness, sonority, etc. (Jakobson & Halle 1956; Kral & Sabol 1989). Focusing on only distinctive features of speech sounds can be first observed around the age of 8–12 months. At that age children develop phonemic categories (the transition from phonetic to phonemic representation), and by that lose the ability to differentiate features of speech sounds that are non-distinctive (Werker & Tees 1984b, 1983). Children thus specialize to the mother language. Attending only to the distinctive features allows us, whenever exposed to the same phoneme, to have the same perception, even though exact acoustical properties of the stimulus differ. Consequently, during the first year of life children learn to abstract phonemic categories based on feature analysis that has already been established.

However, behavioral data indicate that some acoustical feature sensitivity improves post-natally (similar to the visual system): the ability to localize sounds in space is improving during the first 18 months after birth (Morrongiello & Rocca 1987, compare Hillier et al, 1992). Discrimination of speech embedded in noise and discrimination of degraded speech continues to improve over the time-period of 5 years after birth (Eisenberg et al, 2000; Elliott et al, 1979; Elliott 1979). In conclusion, although we are born with some capacity to perform feature analysis, this ability further improves during development.

Once feature maps and representation of auditory objects (like phonemic categories) have been formed, focusing on the previously non-distinctive features becomes difficult and only possible if some sort of their representation is preserved (at least rudimentary) and is accessible—which may not always be the case. That gives rise to what physiologists and psychologists call developmental sensitive periods: periods during which exposure to certain tasks is necessary so as to master them appropriately. Such is the phonetic sensitive period: the ability to learn to categorize sounds to phonemes is largest in the first year of life in hearing children. Later, differentiation of previously non-distinctive features (as in learning new phonetic contrasts) becomes progressively more difficult (Werker & Tees 1984a). As a rule, late-learned languages are mastered only imperfectly, especially if the phonetic systems differ from the mother language significantly (like English-speaking adults learning Chinese or vice versa).

## Sensory deprivation

Sensory deprivation is the absence of sensory input for a significant period of time. During deprivation, mechanisms aimed at adaptation to sensory input may not operate properly and may even become maladaptive. This may consequently lead to development of neuronal networks that are not capable to appropriately represent features of the sensory input (a *naïve sensory system*). Learning of feature discrimination (and their categorization, leading to formation of auditory 'objects') depends on appropriate feature representation and thus may be disabled by the naïve pattern of neuronal networks. Going beyond this classical interpretation, another process can have significant developmental impact (Kral & Eggermont, submitted): once a set of auditory objects has been formed, the child can recognize sounds and differentiate them. At this developmental time, plasticity can be *actively* modulated and controlled by top-down influences based on the needs of the categorization process. The absence of auditory experience disables such processes.

*Prelingual deafness* is defined as deafness that affects a subject before language acquisition. This definition is per se inaccurate, as language acquisition is a gradual process. Also, humans (and some primates) start hearing before birth (Kisilevsky et al, 2000). Pre-natal 'hearing' mainly refers to the speech of the mother, her heartbeat, her digestion, and her breathing, however sounds from outside the mother's body can also activate the auditory system (Sohmer et al, 2001; Sohmer & Freeman 2001). This leads to a condition when the brain is very early (perinatally, possibly even pre-natally) primed to features of the mother language (DeCasper & Fifer, 1980; Dehaene-Lambertz et al, 2002; Locke 1997; Mehler et al, 1988). Such early hearing experience may have consequences for patterning of feature maps, but due to its passive nature is most probably less important for feature categorization in the phonemic domain. In general, passive language presentation (e.g. as demonstrated in hearing children of deaf parents by watching TV for two hours daily) does not suffice for language learning. At least five hours spent in the company of hearing speakers per week ('active' language experience) are necessary for normal language development in such children (Schiff-Myers 1993). Despite all the above reservations, one can define the prelingual (in contrast to postlingual) deafness as a deafness that sets in before the time when language representations (e.g. in form of phonemic categories) 'started' to develop.

*Congenital deafness* is a more strict concept than prelingual deafness, defining a condition when the central auditory system has never had any hearing experience. In prelingual deafness this does not need to be always the case. Such distinction is not purely academic: from the visual system we know that some (even brief) visual experience suffices for initiation of stimulus-induced developmental steps in primary visual cortex, and thus 'a bit' of visual experience is different from no experience (Li et al, 2006). Differentiation of congenital deafness from perinatal deafness is, unfortunately, not always possible in humans.

Spontaneous activity can also trigger developmental processes. During early developmental stages, spontaneous activity in the optic nerve is characterized by a bursting pattern (Wong 1999). Bursts appear in topologically-neighboring places within the sensory epithelium and lead to correlated activity in fibers

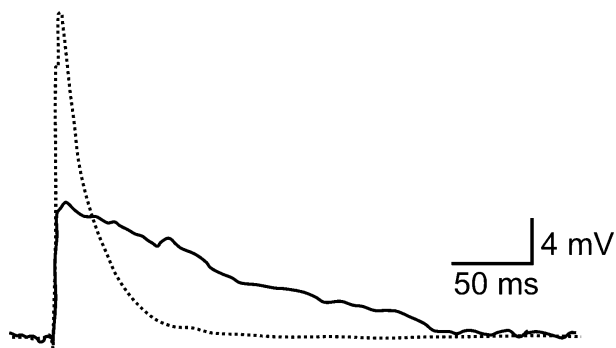
innervating topologically-neighboring cells in the sensory epithelium. That can on its own trigger patterning in the developing afferent sensory systems even in absence of evoked activity. It is assumed that a rudimentary retinotopy can result from this process in the afferent visual system. Spontaneous activity is dependent on the functional status of the sensory epithelium, as its main drive comes from the sensory cells. In the auditory system, bursting can appear at hearing onset in response to sustained acoustic stimulation (Walsh & McGee, 1987). Spontaneous activity in the auditory nerve around birth is very low and does not show spontaneous bursting. However, spontaneous bursting has been observed during embryonal development, as shown in the avian cochlea (Lippe, 1994, 1995), cochlear nucleus of marsupials (Gummer & Mark, 1994), and the midbrain of the bat (Rübsamen & Schafer, 1990). How far this finding can be generalized to the auditory nerve of other animals and humans is not clear. It is not known whether such bursting is associated with propagating waves along the cochlea.

How and which type of deafness affects the spontaneous activity before hearing onset is unclear. The consequences for the central auditory development can therefore not be assessed.

## Development and plasticity

Possibly the most difficult task for the brain is to form its own complex structure and function from a starting point defined by our genetic make up, using experience as a teacher. Learning is the ability to adapt a function of the nervous system (and thus behavior) to external or internal stimuli. The first step of an adaptation of a function in the nervous system consists in changes of synapses (synaptic plasticity). Repeated stimulation of a synapse where presynaptic and postsynaptic elements are activated within a short window ( $\sim 10$  ms) in the order from presynaptic to postsynaptic leads to an increase in synaptic efficacy (synaptic potentiation). If such stimulation is repeated for a sufficient time, the change of synaptic efficacy can last for minutes and even hours (the so called long-term potentiation). Vice versa, an asynchronous or a sparse activation of a synapse leads to the opposite process (long-term depression). This property has been demonstrated in the hippocampus, in the cerebral cortex, and in many other sites in the nervous system. It is, however, not expressed everywhere in the same extent: subcortical plasticity is less prominent than cortical (Suga et al, 2000), and association areas have a higher plasticity than early sensory areas (Diamond & Weinberger, 1984).

In developing animals, due to immaturity of neuronal membranes and ionic channels, cortical postsynaptic potentials are known to have a longer duration (Figure 1, Aramakis et al, 2000). This has the effect of naturally boosting synaptic plasticity, as individual postsynaptic potentials can more easily temporally overlap. Temporal summation can by that cause a strong depolarization of postsynaptic cells. The eventual consequence of this effect is higher plasticity during early development. The concomitant 'adverse effect' is that representation of acoustical features during early development is not possible with high fidelity (Bonham et al, 2004; Eggermont 1996). This is inevitable, as higher plasticity is essential for experience-dependent development. The immature connectivity of juvenile neuronal networks further contributes to the less well expressed feature representations in the primary auditory cortex (field A1).



**Figure 1.** Post-synaptic potentials change in duration and amplitude during post-natal development. Early in development (solid line, post-natal day 8 in rats): the postsynaptic potentials have a smaller amplitude and a significantly longer duration when compared to those in adults (dashed line, shown post-natal day 26 in rats). Data from Aramakis et al (2000), redrawn and modified.

Thus, synaptic plasticity is easily elicited during development, even by a passive presentation of sensory stimuli. In adult subjects, expression of plasticity requires some additional modulational influence: either suppression of inhibition (disinhibition, as in the case of damage of the cochlea restricted to a certain frequency range, Robertson & Irvine 1989; or activation of neuromodulatory systems like the cholinergic input to the cortex, Bakin & Weinberger, 1996; Kilgard & Merzenich, 1998). Thus 'learning' during development differs from learning in adulthood. In the course of cortical development, a massive rearrangement of synaptic organization takes place additionally: after a phase of extensive cortical synaptogenesis (humans, 2–4 years), a synaptic elimination ('pruning') sets in (4–16 years; Huttenlocher & Dabholkar 1997). This process is accompanied by transformation of an immature, 'labile' synapse into a stable one (Benson et al, 2001; Vicario-Abejon et al, 2002). Synaptic maturation is massively modulated by sensory experience, whereas numerous molecular factors play a decisive role (e.g. neurotrophic factors and enzymes degrading perineuronal nets, see Oray et al, 2004).

Many other developmental changes have been reported in the hearing auditory system: the cochleotopic gradient, for example, changes significantly: the same cochlear region stimulates a larger cortical area in young cats and rats when compared to adult animals (Bonham et al, 2004; Kral et al, 2005b; Zhang et al, 2001). Also the temporal properties of cortical units change during post-natal life, showing increasing capacity for entrainment to periodic stimuli (Eggermont, 1996). These and similar findings can be interpreted as a maturational process of feature analysis.

Some authors argue that the neuronal network of the newborn cerebral cortex could first be compared to a blank sheet of paper (a *tabula rasa*; Kalisman et al, 2005) and that it becomes patterned by sensory stimuli only later in life. This appears to contrast with the neurophysiological findings of (at least some) feature detectors that are present before the onset of sensory input. The newborn brain is to a certain extent pre-patterned, partially based on genetic make-up and partially due to prenatal hearing experience (in primates). The extent of the pre-pattern-

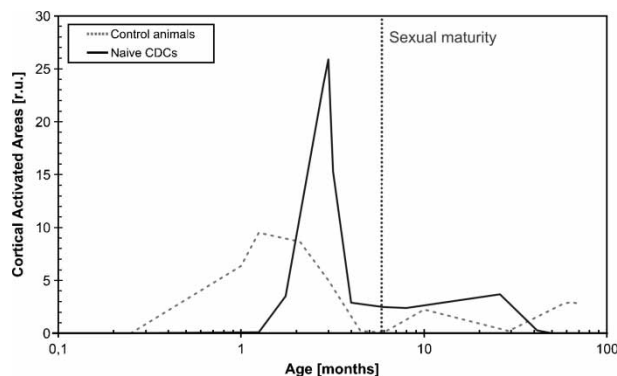
ing will however differ in different cortical areas: higher-order areas may be less patterned than primary ('early') areas.

### Developmental changes in the deaf

To investigate how deafness affects development and the functional properties of cortical neuronal networks, an animal model of controlled and complete deafness from birth is necessary. Complete deafness is observed only following a destruction of the organ of Corti. Such an intervention is, unfortunately, irreversible. Therefore, the only possibility to stimulate the auditory nerve fibers following destruction of the organ of Corti is to do it electrically (via cochlear implants). To allow reproducible electrical stimulation, the auditory nerve fibers must be well preserved. The animal model that best meets these conditions is the congenitally deaf (white) cat (Heid et al, 1998; Mair, 1973; Rebillard et al, 1981; Rebillard et al, 1981). This species shows in 50–75% of the animals inborn (congenital) deafness associated with a complete loss of inner and outer hair cells (and considered some additional supporting structures in the organ of Corti). No signs of significant hearing could be demonstrated during the first month of life in a longitudinal study in those animals (Heid et al, 1998). Therefore, animals selected as deaf after a hearing screening with sounds with 125 dB SPL (Heid et al, 1998) are of completely and congenitally deaf. However, it is noteworthy that their spiral ganglion (housing the cells whose axons constitute the auditory nerve) and the membranous labyrinth are preserved. Even at the age of two years, no signs of spiral ganglion cell loss could be demonstrated in the part of the cochlea into which a cochlear implant can be inserted (Heid et al, 1998; compare Kral et al, 1998). Consequently, in this animal model central responses to electrical stimulation of the auditory nerve are not biased by a pronounced and highly variable degeneration of spiral ganglion cells, as is the case in pharmacologically-deafened animals (where a loss of up to 50–90% of the spiral ganglion cells, depending on age, can be observed; compare Leake et al, 1999). Importantly, developmental studies of central responses are only possible under the assumption of reproducible input, not biased by a changing state of the spiral ganglion cell population.

### Development of the naïve auditory cortex

In congenitally deaf cats, it was, for the first time, possible to follow the functional development of the central auditory system under congenital auditory deprivation (Kral et al, 2005b). The development of response properties in the auditory cortex of electrically-stimulated **hearing controls** was compatible with previously-published data on development of an acoustically-stimulated auditory system. The results have shown that the activated cortical region in field A1 first expands (Figure 2), and after the second month of life shrinks again (Kral et al, 2005b). A similar pattern has been observed also in acoustically-stimulated hearing cats (Bonham et al, 2004), and rodents (Zhang et al, 2001). Functionally, this expansion of the activated area might be related to the expansions and the following refinements in thalamocortical projections and could be important for the developmental adaptations of topologic arrangement of thalamocortical projections. Developmental changes of cochleotopic organization were shown to be dependent on



**Figure 2.** Post-natal development of cortical activation area determined with cochlear implant stimulation in normal hearing controls and in congenitally deaf cats (CDCs). Cortical activation area was determined by the maximal positive amplitude (Pa wave) of the local field potential recorded with glass microelectrodes at  $>100$  cortical positions. In hearing controls the area shows a correspondence to development of synaptic numbers in the primary visual cortex. In deaf animals a delay in the early peak, its amplitude, and a more pronounced decrease was observed. For interpretation see text. Data taken from Kral et al (2005b), figure modified.

early manipulations (Harrison et al, 1991; Nakahara et al, 2004; Zhang et al, 2002). Morphology of cortical local field potentials showed a developmental pattern well comparable to the development of individual neuron response properties in acoustically-stimulated hearing cats (compare Kral et al, 2005b, with Eggermont, 1996). Here, middle-latency responses showed most dramatic changes within the first eight weeks of life, with fastest changes within the first month (Kral et al, 2005b). Long-latency responses ( $>100$  ms) showed a developmental pattern continuing up to the onset of puberty in cats (4–6 months, Kral et al, 2005b).

The primary auditory cortex is organized in vertical columns, spanning over all six neocortical layers (Abeles & Goldstein Jr., 1970). Within these columns, activity is known to progress in a patterned and reproducible way (Mitani et al, 1985; Mitani & Shimokouchi, 1985). Laminar-specific profiles of gross synaptic activity, revealed by current-source-density analysis of local field potentials, demonstrated that significant activity in deep ('output') cortical layers V and VI develops within the first 2–3 months after birth (Kral et al, 2005b). The pattern comparable to adult (hearing) control animals, with fine-structure (in time and layer), appeared around the 3<sup>rd</sup>–4<sup>th</sup> month of life in hearing cats. Unfortunately, for this developmental data no corresponding findings with acoustical stimulation exist at the moment.

A different developmental pattern was observed in **congenitally deaf animals**. The primary auditory cortex showed responsiveness to early auditory stimulation through a cochlear implant (first local field potentials with long latencies were recorded on day 8 post-natally, Kral et al, 2005a), despite congenital deafness. This responsiveness was preserved until adulthood. The development of both surface-recorded local field potentials, the extent of the cortical activation area (Figure 2) as well as laminar profiles, demonstrated a delay of 1–2 months in deaf cats, with some persistent deficits in long-latency responses,

with a delay in responses within supragranular layers (II and III), as well as a reduction in activity within deep cortical layers.

These data could for the first time demonstrate that congenital deafness has a deep functional impact on the development of the primary auditory cortex. Thus, post-natal development is dependent on experience: it is not only modulated by deviant hearing experience, it also requires hearing for its basic functionality.

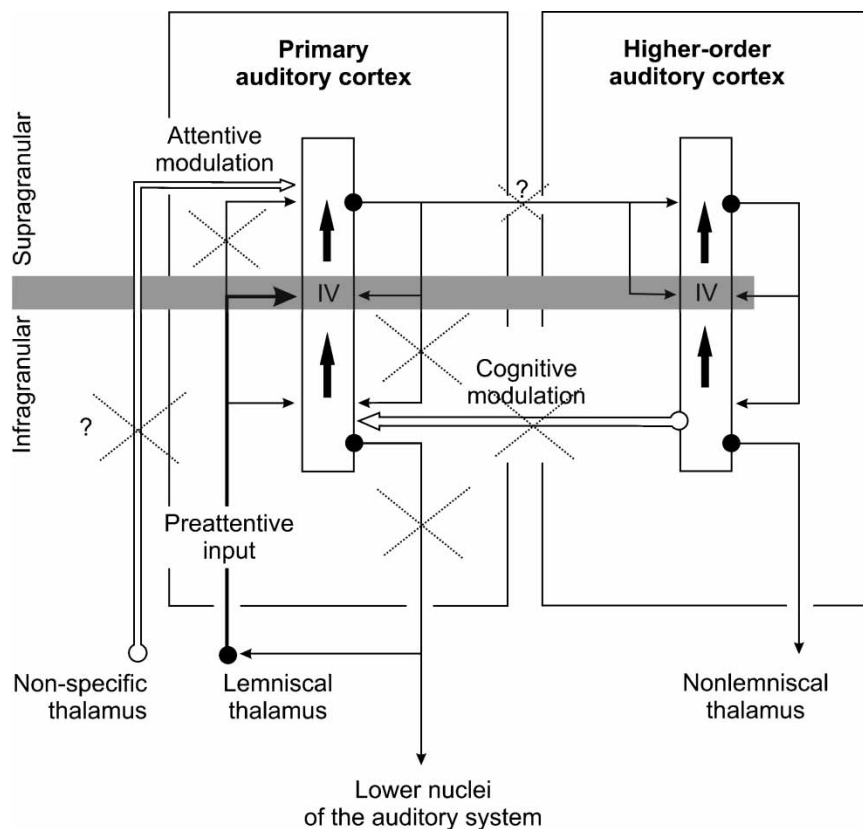
### Naïve auditory cortex in adults

In adult animals, rudimentary feature sensitivity could be demonstrated both in congenitally- as well as in neonatally-deafened cats. A rudimentary cochleotopy in the primary auditory cortex (field A1) of congenitally deaf cats was demonstrated despite many months of deafness (Hartmann et al, 1997). Also when compared to hearing controls (after hair cell destruction and with stimulation via cochlear implants) the rate-intensity functions as well as latency-intensity functions and some other properties were preserved (Raggio & Schreiner, 1994, 1999; Schreiner & Raggio, 1996). Recently, first results on binaural properties of the units in the field A1 of congenitally deaf cats demonstrated some (although very rudimentary) binaural feature sensitivity preserved despite long deafness (Kral et al, 2006a). These results are in accord with previous studies showing binaural sensitivity of individual neurons in primary auditory cortex of kittens established very early during development, even before the hearing thresholds have declined under 100 dB SPL (Brugge et al, 1985, 1988).

In total, at least rudimentary features of response properties, and also some of the feature detectors in the auditory cortex, are preserved despite a complete lack of auditory experience.

The cortical threshold to electrical stimulation showed a tendency for lower values in neonatally deafened cats than in hearing controls (Raggio & Schreiner, 1999). In congenitally deaf cats the results reached statistical significance (Kral et al, 2005b). The difference in the level of significance may be the consequence of a varying and pronounced degeneration of spiral ganglion in neonatally-deafened cats. The result has important implications: the 'deaf' primary auditory cortex becomes 'hypersensitive' to peripheral (at least electrical) stimulation. One interpretation is a down-regulation of inhibition in the cortex, which indeed has been observed indirectly by means of current source density analysis (Hubka et al, 2004; Kral et al, 2005b). Nonetheless, this is not a sufficient explanation, as inhibition is effective with increasing intensity of the input, and at threshold intensity its effect is (as a rule) limited. The hypersensitivity must be additionally related to a change in the excitatory synaptic transmission and to a naïve pattern of the constituting neuronal networks.

Using the technique of current source density analysis of local field potentials, the classical activation pattern of the cortical column could be well reconstructed in hearing electrically stimulated controls (Figure 3, see Kral et al, 2000). It indicated that activity progresses from input layer IV to layers II/III (supragranular layers) and from those latter to layers V and VI (infragranular layers). Layers V and VI ('output layers') send long-ranging connections to subcortical auditory structures (feedback projections). Higher-order cortical areas project back to the primary auditory cortex, mainly to layers V and



**Figure 3.** Model of the deficits in the auditory cortex in deaf: Lemniscal input targets in the field A1 mainly layer IV (grey bar), but also supragranular and infragranular layers. Neurons in infragranular layers project to layer IV, layer IV projects to supragranular layers. Supragranular layers project back to layer IV and infragranular layers ('folded feedback'). Infragranular layers send descending fibers to subcortical nuclei. Feed-forward coupling to the higher-order auditory areas is accomplished via supragranular layers, descending projections from higher-order cortex target the infragranular layers in A1 ('cognitive modulation'). Based on Raizada & Grasberg, 2003. Dashed crosses show which connections are supposed not functional in congenitally deaf cats; based on data from Kral et al, 2000, 2005, 2006.

VI. Thus, these output layers integrate intrinsic input from within the cortical column after some processing with direct input from the auditory thalamus and with descending inputs from higher-order areas (so-called cognitive modulation of activity, Raizada & Grossberg, 2003; Shuler & Bear, 2006). At a comparable above-threshold intensity, the synaptic activity within the cortical columns in congenitally deaf cats was significantly reduced and the layer-specific pattern was altered (dashed crosses in Figure 3). Activation of supragranular layers was delayed and a marked reduction in infragranular cortical layers was noted (Kral et al, 2000, 2001). The cortical column itself appears no longer competent to sufficiently activate the deep cortical layers. One possible consequence of this finding is that the cortex can no longer incorporate cognitive modulatory influences. These are important for influencing 'early' cortical activity in primary areas depending on the demands of categorization of features into auditory events ('objects') and by that influencing (directing) experience dependent plasticity (Ahissar & Hochstein, 2004; Hochstein & Ahissar, 2002).

One reason for the reduction of activity in infragranular layers is a desynchronization of columnar activation: synchronous activation of several cortical layers within a short time window is essential for proper function of neurons in infragranular layers

that can then produce a burst of action potentials (Larkum et al, 1999, compare also Llinas et al, 2002). If these inputs are desynchronized, the activity of neurons in deep cortical layers drops, and bursts are not produced. The above described delay in activation of supragranular layers relative to layer IV in deaf animals could contribute to the reduction of activity in deep cortical layers (Kral et al, 2000, 2005b, 2006b). Using independent component analysis of local field potentials, further desynchronizations of activity at the microcircuitry level could be observed in field A1 of adult congenitally deaf cats (Hubka et al, 2004). Breakdown of synchrony within the primary auditory cortex is one important reason for the deficits observed in adult animals.

In total, the results indicate substantial deficits in the propagation of activity within the primary auditory cortex, but also point to deficits in the interaction of primary with higher-order cortical areas. One interpretation of the results is that congenital deafness leads to a functional de-coupling of field A1 from descending inputs from higher-order cortical areas that target the infragranular layers (Kral et al, 2006b, 2005b). Provided that the input to the infragranular layers from within the same column is decreased due to the delay in activation of supragranular layers, and due to a weaker or absent input from

the higher-order auditory cortex, these layers are not sufficiently activated. This has an important consequence as, as shown above, top-down interactions are cardinal in the emergence of higher-order categories and their influence (modulation) on low-level feature maps and by that also on their adaptive plasticity. As we shall see below, this interaction is further compromised by cross-modal reorganization of higher-order auditory areas.

### Cross-modal plasticity in the 'deaf' auditory cortex

What is the function of the auditory cortex in absence of auditory input? The cerebral cortex, especially during development, is very plastic: after early aspiration (destruction) of the inferior colliculus the primary auditory cortex can reorganize to process visual activity (Pallas et al, 1990; Roe et al, 1992). Responses in the primary auditory cortex of hearing animals do not necessarily have to be evoked only by sounds: In hearing monkeys highly-overtrained to an auditory categorization task, activity evoked by visual stimuli and movements of the monkey related to subsequent sound presentation can be recorded in primary auditory areas with relatively short latency (Brosch et al, 2005). Units in primary visual cortex also do not code only the physical attributes of visual stimuli: responses predicting reward but not directly related to visual stimuli have been found in deep (infragranular) cortical layers of rat field V1 (Shuler & Bear, 2006). That also demonstrates that top-down influences can strongly operate on the early (primary) sensory areas. Provided with this multitude of influences, does the 'deaf' primary auditory cortex cross-modally reorganize?

In subcortical nuclei, significant dystrophic changes appear in deafened or congenitally-deaf cats (Heid, 1998; Hultcrantz et al, 1991; Saada, et al, 1996; Shepherd & Hardie, 2001; Trune, 1982), which makes a take-over of a new function improbable. In fact, this has not been described so far in deafness, despite the fact that somatosensory inputs into the auditory pathway exist. But cerebral cortex shows a more extensive connectivity and is endowed with higher plasticity than subcortical nuclei.

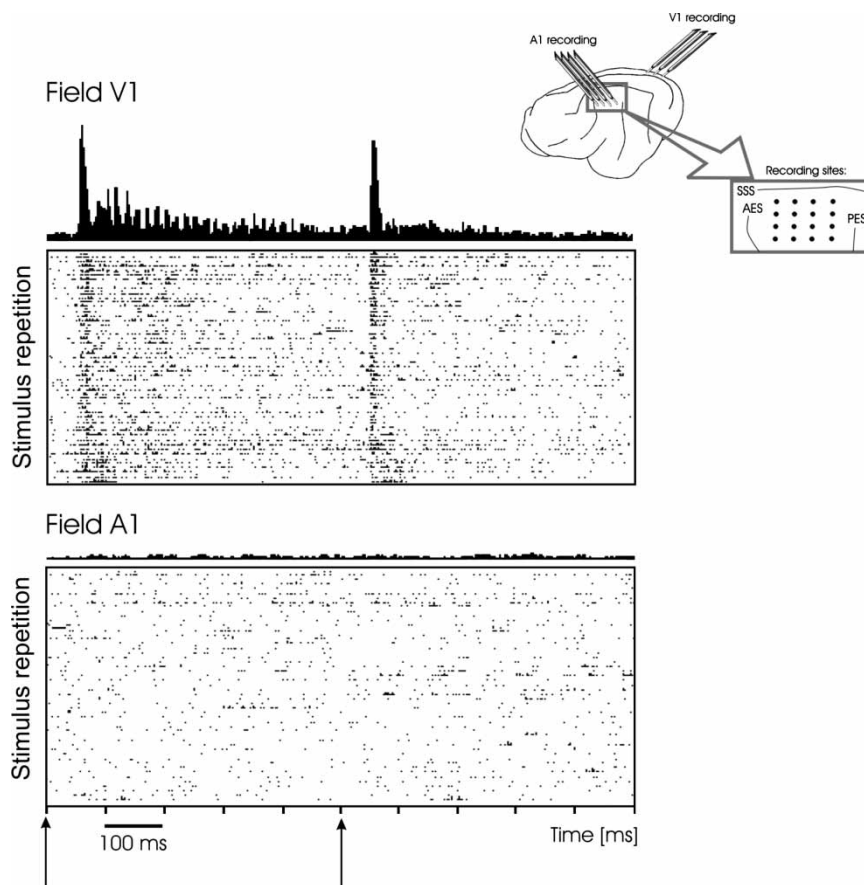
A first investigation on visually evoked activity in the primary auditory cortex of an awake congenitally deaf cat showed that there were no unit responses to visual flashes (Stewart & Starr, 1970). Some years later the same stimulus was reported to generate local field potentials in the primary auditory cortex of these animals even in general anaesthesia (Rebillard et al, 1977, 1980). To resolve this discrepancy attempts to replicate the latter findings in more controlled conditions were undertaken (Kral et al, 2003). In addition to visual flashes the last study incorporated also a stimulus that includes both pattern and motion: phase-reversal gratings of different orientations and spatial frequencies. Additionally, to exclude biasing peripheral factors, the refraction of the eyes was measured and compensated for with contact lenses. The location of the fovea was back-projected to a screen. Visual stimuli were delivered to the fovea via a computer screen, and outside of the fovea using manually-presented moving light bars of different orientations. Visually-evoked local field potentials were identified; however they were of small amplitude. Current source density analysis did not reveal any generators of these potentials within the field A1. No unit responses to the visual stimuli were found in field A1, despite simultaneous strong responses in field V1 (Figure 4). The findings are in agreement with the interpretation that the

visually-evoked field potentials in congenitally deaf cats were in fact far field effects of activity outside field A1. The study of Kral et al (2003) thus supports the previously-described absence of visual activation in field A1 of an awake congenitally deaf cat (Stewart and Starr, 1970), as well as another study of Hartmann et al (1997), who reached the same conclusion using stimulation with an array of light diodes positioned right in front of the eyes.

However, that does not mean that there is no cross-modal reorganization in the auditory system of these animals: behavioral experiments with congenitally deaf cats demonstrate that they outperform hearing controls in a visual motion detection task and motion detection of a flashed visual stimulus in the peripheral visual field (Lomber & Kral, unpublished data), demonstrating cross-modal compensation. This does most probably take place at some level of the auditory cortex outside field A1. Also, other sensory inputs can recruit the auditory system in congenitally deaf: although few studies are available, some evidence exists that somatosensory input can evoke activity in the auditory cortex (Levanen et al, 1998). Differentiation on whether primary areas were involved was not possible: the source reconstruction placed the activated area in the higher-order cortex, however, that does not mean that activation of primary areas was excluded.

Which functions are possible candidates for recruiting the deaf auditory cortex is difficult to say: topological neighborhood in the cortex is only one possible criterion.

Several investigators have demonstrated recruitment of the auditory cortex by visually-presented sign language in deaf subjects, but not hearing controls understanding sign language (Nishimura et al, 1999; Petitto et al, 2000, 2001). Later investigations supported that this difference is specific to auditory areas and is not detectable in visual areas (Fine et al, 2005). Interestingly, this cross-modal reorganization was restricted to non-primary areas (Figure 5). The only study demonstrating an additional involvement of the right primary auditory area (but not the left one) reported some voxels falling into the primary areas based on probabilistic maps (Finney et al, 2001). A very interesting aspect on the latter study is that this cross-modal reorganization is not only restricted to linguistic visual stimuli, but is detectable also with non-linguistic moving visual stimuli (*ibid.*). Further support on the cross-modal reorganization of the auditory cortex comes from the spontaneous glucose metabolism detected in congenitally-deaf children with positron emission tomography (PET), (Lee et al, 2001). Here, all figures show the lateral view of the brain without focusing on activity in depth of the Sylvian sulcus, in which primary auditory areas are located. The data in this study support the notion of a gradual recruitment of higher-order auditory areas by some non-auditory tasks, whereas a trade-off between this recruitment and the performance after cochlear implantation is implicated (*ibid.*). Similarly another PET study indicates a direct negative interference between auditory and visual modality post implantation (Nishimura et al, 2000). In accordance with these considerations, prelingually-deaf adults are superior in visual performance (motion detection in periphery of the visual field) when compared to hearing controls (review in Bavelier & Neville, 2002). These data correspond well with both behavioral and neurophysiological findings in congenitally deaf cats, further emphasizing the suitability of this animal model.



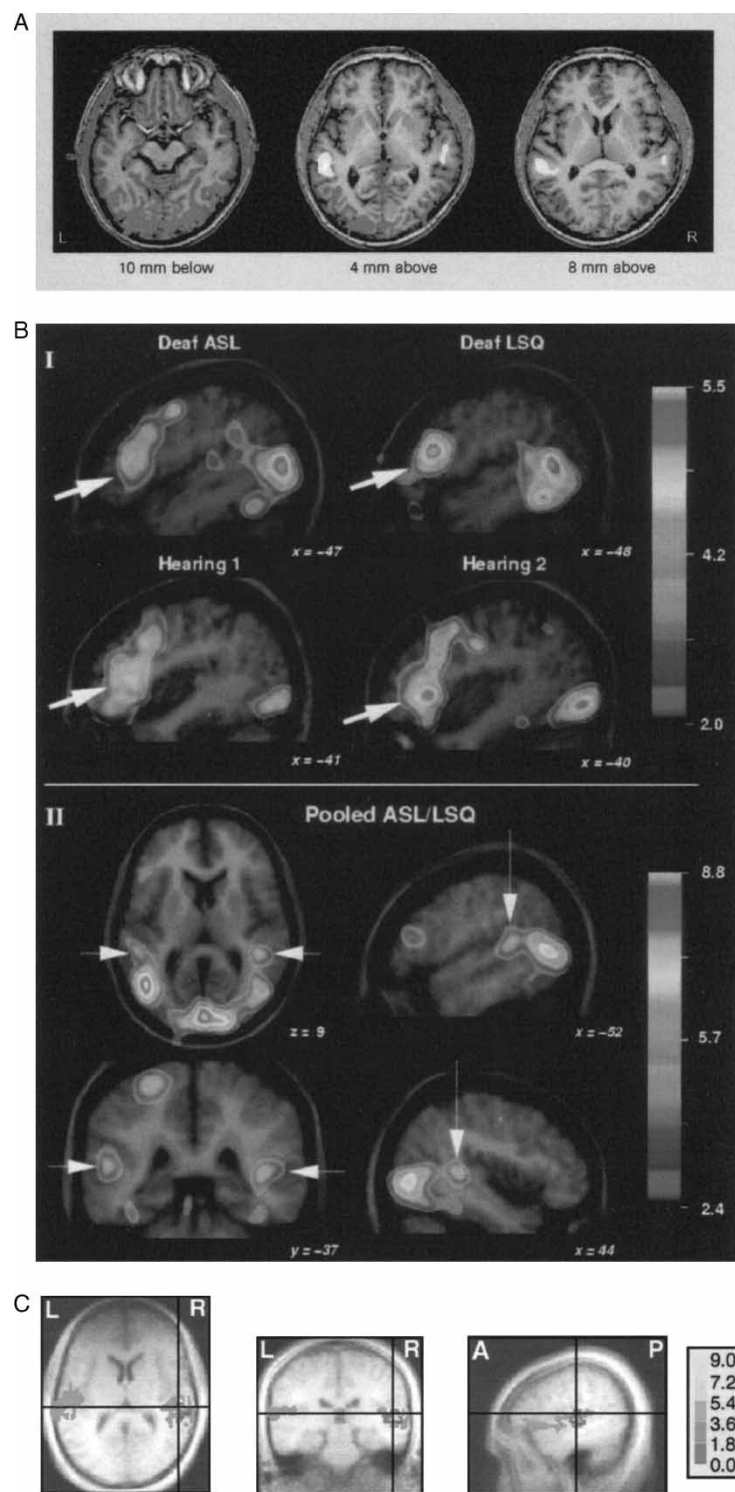
**Figure 4.** Absence of visual responses in the auditory cortex of congenitally deaf cats under stimulation with phase-reversal gratings (lightly anaesthetized preparation). Inset shows position of recording electrodes in primary visual and primary auditory cortex (4+4). Both in hearing controls and congenitally deaf cat's similar response patterns were obtained. Top: Example of a response in primary visual cortex. Post-stimulus time histogram and raster plot of the individual response trials are shown. Time of phase reversal is marked at the abscissa by arrows, two reversals per trial. Strong responses are observed. Bottom: Absence of a response in primary auditory cortex. Modified from Kral et al (2006), data from Kral et al (2003).

If we combine all the available evidence, it becomes clear that there is a difference in the extent of cross-modal reorganization between primary and higher-order cortical auditory areas. Although higher-order areas cross-modally reorganize and learn to process visual stimuli (also non-linguistic!), this effect is much weaker (if present at all) in the primary areas. Combined with the lack of evidence for cross-modal reorganization of primary auditory areas in animal research, where a more exact delineation of the different areas is possible, we can conclude that cross-modal reorganization is significant only in higher-order auditory areas.

There is still controversy to what extent the primary auditory cortex of untrained *hearing* subjects can be activated by visual stimuli; this has been shown only in hearing monkeys highly-overtrained to an audio-visual task (Brosch et al, 2005). Here the 'visually-evoked' responses appeared only if they directly predicted an auditory stimulus. This is not a condition that can be extrapolated to congenitally deaf subjects. If an activation of the auditory cortex by visual stimuli alone is present also without extensive training, it will be at most weak. A weak visual (heteromodal) drive alone will not suffice to induce cross-modal reorganization of the auditory cortex, as sparse synaptic

activations are at the synaptic level more likely to elicit long-term depression than long-term potentiation. A reorganization towards visually-induced activity will be possible only with a coordinated audio-visual stimulation (as in the study of Brosch and collaborators), which, due to additional auditory inputs, drives the cortical cells above threshold and allows heterosynaptic induction of long-term synaptic potentiation of visual inputs. The auditory drive is absent in deaf subjects. That explains why cross-modal reorganization appears to be focused on higher-order areas and much less (if at all) found in early (primary) areas in deaf subjects. A first study systematically addressing this point in the primary auditory cortex of awake primates with auditory and somatosensory stimulation demonstrated that the effect of somatosensory stimulation alone is very weak on the 'hearing' primary auditory cortex (Lakatos et al, 2007). However, after pairing this stimulus with an auditory stimulus, supralinear summation was found. This supports the hypothesis that primary auditory cortex receives only a very weak heteromodal input, and to evoke cross-modal plasticity this input needs an intact auditory input coherent with the heteromodal input.





**Figure 5.** Imaging studies did not consistently demonstrate recruitment of primary auditory cortex in congenitally deaf: (A) Nishimura et al (1999): ‘sign language activates the ‘language’ areas but not primary auditory cortex’. Reprinted by permission from Macmillan Publishers Ltd: *Nature* 11(4): 811–815, Copyright 1999. (B) Petitto et al (2001): ‘rCBF peaks reported here for deaf signers fall posterior to Heschl’s gyrus (as is also evident in the horizontal and sagittal sections of *B II*)’. Reprinted with permission from *Proc Nat Acad Sci USA*, copyrights National Academy of Sciences, USA. (C) Finney et al (2000): ‘... in the right ROI ... several voxels ( $0.22 \text{ cm}^3$ ,  $\sim 23\%$  of the total region of the effect) fell within area 41 (primary auditory cortex), which encompasses the medial portion of Heschl’s gyrus’. Here, the technical details of the probability map reconstruction have to be taken into account (for details, compare discussion in Kral et al, 2003). Also, the effect was found only at the right hemisphere. Reproduced with permission from Macmillan Publishers Ltd: *Nat Neuroscience* 4(12): 1171–1173, Copyright 2000.

## Hearing after congenital deafness: unimodal plasticity

The auditory system, as all sensory systems, is capable of remarkable unimodal plasticity. Despite many differences in the pattern of acoustically evoked activity in a hearing cochlea when compared to electrically-evoked activity in a deaf cochlea (Kral & Tillein, 2006), even adults can easily adapt to this type of stimulation and learn to understand speech.

In young prelingually deaf children, adaptation to cochlear implants is more extensive and fast when compared to teenagers as the capacity for neuronal plasticity is largest during development (review in Kral & Tillein, 2006). Such adaptation involves subcortical plasticity (Snyder et al, 1990, 1991) as well as extensive cortical plasticity (Klinke et al, 1999; Kral et al, 2001, 2002, 2006b). The cortical plasticity includes a reorganization of cortical microcircuitry in primary auditory cortex with increasing area of cortical activation (Klinke et al, 1999, 2002), increasing amount of synaptic activity with stimulation duration (Kral et al, 2006b), increasing synchronization of activity between cortical layers (Kral et al, 2006b), and recruitment of deep cortical layers (Klinke et al, 1999; Kral et al, 2006b). These reorganizations can consequently lead to increasing activation of higher-order cortical areas, and also lead to an increase in activity in the corticofugal system. Based on current findings in the hearing auditory system (Sakai & Suga, 2002) we assume that the cortical reorganization is the source of subcortical reorganizations and not vice versa (for discussion, compare Kral & Tillein, 2006). Cortical reorganization after cochlear implantation in humans has been shown to extensively include higher-order areas (Giraud et al, 2001; Giraud et al 2001; Ito et al, 2004; Lee et al, 2001; Naito et al, 1997).

Whereas responses in the primary auditory cortex can be recorded shortly after implantation in prelingually deaf children, the recruitment of higher-order auditory areas by cochlear implant stimulation is increasing gradually in the course of hearing experience (Naito et al, 1997; Nishimura et al, 1999). Although the primary auditory cortex shows a massive reorganization with hearing experience after cochlear implantation (see above: Klinke et al, 1999; Kral et al, 2002, 2006b), strong responses in supragranular layers and layer IV can be detected also in naïve animals (Klinke et al, 1999; Kral et al, 2000, 2001, 2005b). Cochlear implant recipients activated primary and higher-order auditory areas in both postlingually deaf and early-implanted prelingually-deaf subjects after long-term hearing experience (Naito et al, 1997; Nishimura et al, 1999). Higher-order areas were recruited significantly less by long-term hearing experience in late-implanted prelingually-deaf subjects (Naito et al, 1997). These data support the hypothesis that bottom-up and top-down corticocortical connections mature and become patterned by auditory input in early-implanted subjects (Kral et al, 2006b).

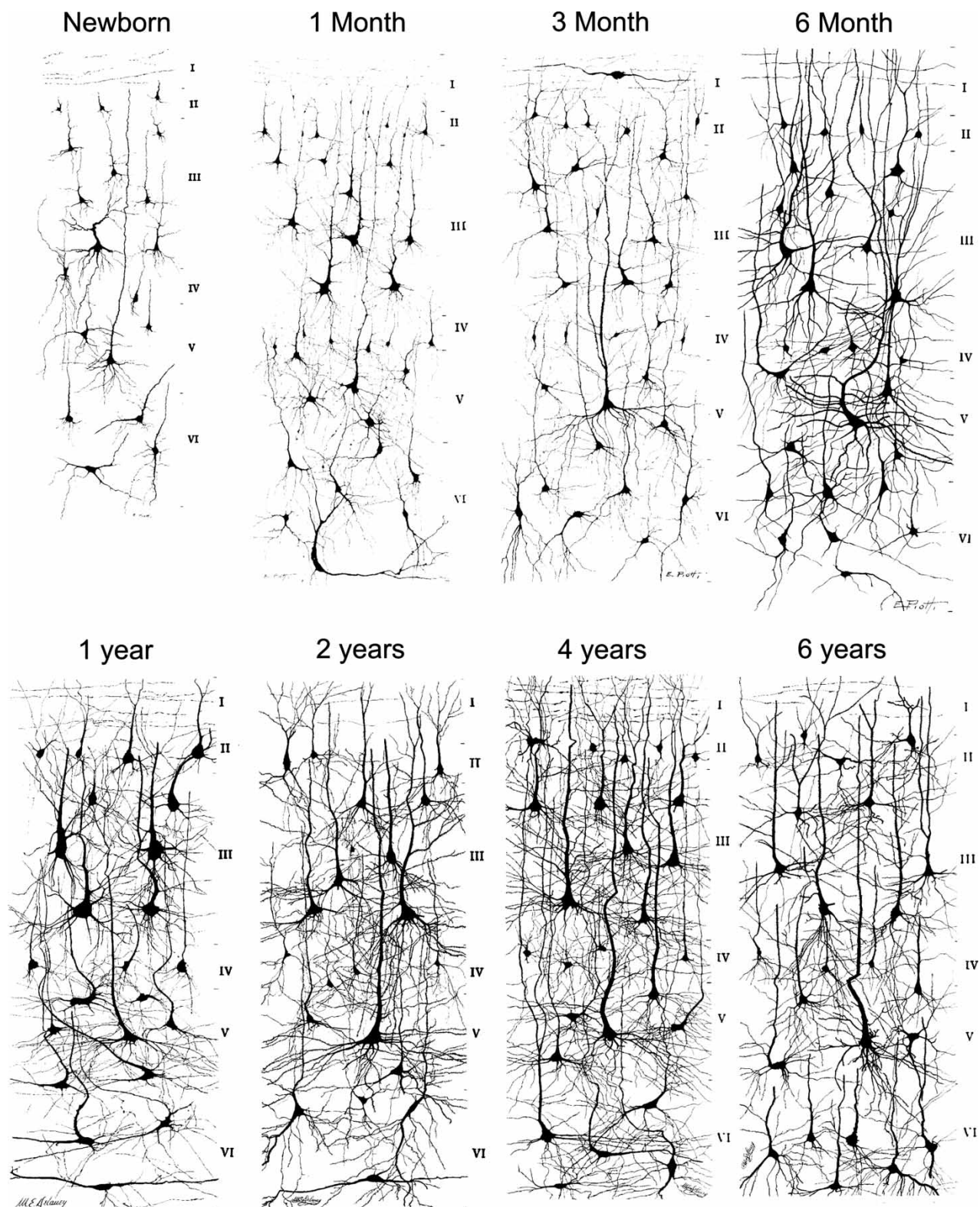
The learning to cope with a cochlear implant is thus bound to developmental sensitive periods, similar to the normal linguistic development (see above). Children implanted before the age of five years perform better in language tests than children implanted later (Fryauf-Bertschy et al, 1997), and adult-implanted prelingually-deaf subjects do not reach an acceptable language competence despite years of training (Busby et al, 1992, 1993). A neurophysiological correlate of this sensitive period has been identified in congenitally deaf cats (Kral et al, 2001, 2002): plastic reorganizations in the primary auditory cortex after cochlear implantation and chronic electrostimula-

tion decreased with increasing implantation age. Corresponding to this finding, electroencephalographic investigations in cochlear-implanted children demonstrate a decreasing amount of plasticity with increasing age (Sharma et al, 2002, 2002a, 2005).

Electroencephalographic data further support the hypothesis of patterning the bottom-up and top-down cortical interactions during the sensitive period: Prelingually deaf children after early cochlear implantation show an increasing amplitude and decreasing latency of wave P1 and an appearance of wave N1 with cochlear implant stimulation (Sharma et al, 2002b; 2005), whereas late-implanted children, especially those implanted in late teens, do not develop wave N1 (Ponton & Eggermont, 2001). Using intracranial recordings of evoked potentials, the generators of wave N1 have been identified mainly in higher-order auditory areas, whereas P1 is generated both in primary and higher order areas (Liegeois-Chauvel et al, 1994). Consequently, the data on implanted children further support the theory that higher-order cortical areas are gradually-recruited by the hearing experience, and are essential for success of cochlear implantation.

There is in fact a multitude of mechanisms leading to sensitive periods in auditory development. There are genetically-based molecular developmental changes taking place in the cortex, and these lead to a decrease in synaptic plasticity (reviewed, e.g. in Kral & Tillein, 2006). On the other hand, the neuronal circuits in the cerebral cortex also change during development. Complexity of dendritic trees changes massively in human auditory cortex, showing a peak at the age of ~4 years (Figure 6; Conel, 1939–1967). Afterwards, the level of their complexity decreases. Later studies confirmed this process concerning synaptic density level, using electron microscopy (e.g. Huttenlocher & Dabholkar, 1997). The newborn cerebral cortex starts post-natal development with a smaller number of synapses. The synaptic counts, however, increase massively during the first years of life (post-natal synaptogenesis), reaching a peak between 2–4 years, to decrease afterwards (until adolescence, to 50% of the peak densities, *ibid.* reference). As synapses are information-processing elements of the brain, the computational capacity of the cortex changes accordingly. The theory of synaptic selection (Changeux & Danchin, 1976) suggests that the brain builds up so many synapses during development that it can not maintain them on a long-term scale. Such synaptic ‘overshoot’ is meaningful, as it makes the brain very adaptable, capable of coping with many different environmental conditions. However, once the sensory system is confronted with certain conditions, it specializes: those synapses that are not needed in order to cope with the environment (those that are not activated) are eliminated (‘pruned’), and only those that are repeatedly activated become stabilized. Molecular mechanisms of these processes have also been described (e.g. Oray et al, 2004).

But what happens to synaptic densities (and neuronal branching patterns) in case of congenital deafness? No synapses (presumably) are activated in the primary auditory cortex. The theory would predict an exaggerated synaptic elimination. However, the investigations on congenitally deaf cats suggest also something else: When gross synaptic currents are considered as a measure of synaptic densities and of synchronicity of synaptic activity, synaptogenesis appears to be delayed and exaggerated in deaf cats, followed by a functional synaptic elimination (Kral et al, 2005b). This is in agreement with results of morphological studies of synaptic densities within area V1 in



**Figure 6.** Development of neuronal morphology in human primary auditory cortex, Conel (1939–1967). Dendritic complexity shows an increase during post-natal development corresponding to later-described increases in synaptic densities. Peak of dendritic morphology (and also synaptic densities) is observed at 2–4 years in hearing subjects, with a decrement afterwards. Developmental changes in these parameters in congenitally (or prelingually) deaf subjects are unknown. Reprinted by permission of the Publisher from the *Postnatal Development of the Human Cerebral Cortex*, Vols I–VIII by Jesse LeRoy Conel, Cambridge, Mass: Harvard University Press, Copyright © 1939, 1975 by the President and Fellows of Harvard College.

neonatally enucleated (blind) kittens (Cragg, 1975; Winfield, 1981, 1983). However, the time when synaptogenesis ceases corresponds to the time when the sensitive period start closing (Kral et al, 2005b). For this reason we assume that although synaptogenesis demonstrates the strongest effect in deprivation, onset of synaptic elimination marks the point that stabilizes functionally incompetent neuronal networks. If inappropriate synapses are being functionally eliminated, activity is reduced and its synchrony is disrupted. The ultimate consequence is that evoked activity (if stimulated using cochlear implants) ceases within intrinsic microcircuits in the auditory cortex and the starting point for plastic adaptations is compromised. As at the same time the phase of massive synaptogenesis has already expired, new synapses can not be formed in extensive manner any more. Under such a condition, associated with a decreasing synaptic plasticity during the same developmental period, the possibility of a reorganization of these networks later in life is substantially compromised.

One can conclude: the naïve auditory system in early development demonstrates rudimentary feature analysis. However, in absence of hearing experience, this feature representation degenerates to a rudimentary level and the intrinsic micro-circuitry shows an incompetence to integrate afferent and top-down influences at the level of primary auditory cortex. Higher-order areas, due to their strong inputs also from non-auditory areas, take-over new functions and undergo cross-modal reorganization. At the same time *early (primary) sensory areas de-couple from the top-down influence of higher-order areas* (Kral et al, 2005b, 2006b). That all together gives rise to sensitive periods in the auditory system.

Sensitive periods in plastic reorganization of the sensory cortex do not imply that there is no plasticity in the sensory cortex after sexual maturity is reached. However, if the sensitive window expired without appropriate sensory input, the naïve auditory cortex could not be appropriately 'patterned', and synapses critical for representation of distinctive features have been lost during development. The naïve cortex therefore can not properly handle the incoming activity, so that adult plasticity can not focus on biologically relevant features. By that and the additional de-coupling from the higher-order influences, plasticity can not be controlled, becomes maladaptive, and learning ability thus limited.

## Conclusions

Based on the data discussed here we propose:

1. During post-natal development, cortical neuronal networks develop at the level of intrinsic microcircuitry (within one area) and also at the level of extrinsic circuitry (between areas). In absence of auditory experience, deficits in intrinsic microcircuitry and data on cross-modal plasticity strongly indicate that back-projections from higher-order auditory areas to the primary auditory areas do not develop properly. By that, cognitive modulation of the primary auditory cortex becomes significantly compromised. Higher-order auditory areas additionally reorganize cross-modally, acquiring visual (and possibly other) functions. Cochlear implantation has to overcome this deficit, and that is only possible provided that the cortex still shows juvenile (large) synaptic plasticity and

the synaptic development had not entered the phase of synaptic elimination (2–4 years of life).

2. Cross-modal reorganization may hinder the processing of auditory stimuli in two aspects: First, by occupying higher-order auditory areas with visual functions which are not only linguistic, but also more elementary, related to visual motion. That complicates the re-utilization of the networks in higher-order areas for auditory functions. Second, the de-coupling of the primary areas from descending modulation (Kral et al, 2005b, 2006b) complicates the cognitive modulation of plasticity in primary areas, and thus the controlled adaptation to incoming activity.
3. From the Piagetian point of view, language develops hand in hand with other cognitive functions and can be learned by a child only if other cognitive abilities are acquired. From this point of view, using sign language might appear to be a good starting point for prelingually deaf children to build up higher-order linguistic representations that can be later re-utilized in learning language via cochlear implants. Some authors claimed that spoken language learning in hearing children of deaf parents is in part based on first learning sign language from their deaf parents. However, more recent analyses indicate that this in fact is not the case (Schiff-Myers, 1993). The described situation is additionally not comparable to prelingual deafness, as hearing children do not suffer from the above-described functional deficits in the auditory cortical areas and also do not undergo a cross-modal reorganization such as deaf children do. In cochlear implant users a negative interference between auditory and visual modality within the auditory areas has been demonstrated (Nishimura et al, 2000). In our view, this interference is the consequence of different representations of the sign language and spoken language at the earliest level of auditory and linguistic representation (phonetic). Higher-order areas, if occupied by visual representations, would have to re-learn to represent auditory information after cochlear implantation. These higher-order areas would not be able to make use of the already established visual representations if these representations are not mutually compatible with auditory inputs. The negative interference obtained in imaging data reviewed above supports this interpretation. Such an effect could hinder the benefit of cochlear implantation. Consequently, emphasizing mainly the auditory channel of communication can be considered as the appropriate therapeutic approach in prelingually-deaf cochlear-implanted children. On the other hand, cross-modal information represented compatibly with the incoming auditory signal, like that obtained from lip-reading (where the temporal structure corresponds to the acoustic signal low-passed in the temporal domain), could be helpful as an additional cue for phonetic analysis of the signal (Calvert et al, 1997). The most important precondition for success is an early cochlear implantation, best before the normal synaptogenesis terminates (2<sup>nd</sup>–4<sup>th</sup> year of life).

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