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Auditory cortical plasticity under operation: reorganization of auditory cortex induced by electric cochlear stimulation reveals adaptation to altered sensory input statistics

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Abstract

We introduce a framework based on plastic-adaptational processes for an interpretation of electrical cochlear implant (CI) stimulation. Cochlear prostheses are used to restore sound perception in adults and children with profound deafness. After providing a review of cortical plasticity, we summarize our findings using optical imaging of intrinsic signals to map cat auditory cortex (AI) activated by CI stimulation. In adult AI of neonatally deafened animals, the acoustic deprivation caused a severe distortion of cochleotopic maps. A three-month period of CI-stimulation using the *continuous interleaved sampling* strategy did not re-install the status typically found in normal adults, but resulted in the emergence of a new topographical organization characterized by large, joint representations of all stimulated electrode sites. We suggest that the effectiveness of CI-stimulation relies primarily on a re-learning of input pattern arising from "artificial" sensory inputs via electrical stimulation, thereby supporting the importance of learning and training for the interpretation and understanding of the effects of CI stimulation. We suggest that the ability for gaining/re-gaining speech understanding mediated by CI-stimulation is accomplished by new strategies of cortical processing due to enhanced cooperativity among large populations of neurons that serve higher processing stages to interpret new patterns arriving from the periphery. These strategies are thought to emerge from adaptational capacities in response to the constraints imposed by the properties of the new input statistics that in turn result from the stimulation strategy employed.
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1. Introduction

For many years, cochlear prostheses have been used to restore sound perception in patients with profound sensorineural deafness. By electrically

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stimulating acoustic nerve fibers, the central auditory system can be activated in a systematic way that maintains the capacity for hearing. A first account of this approach can be traced back nearly half a century (Djourno and Eyries, 1957). Utilizing the critical period for speech acquisition, clinical data suggest that children implanted before 2 years of age have an excellent chance of acquiring speech understanding (Graham, 1988; Tyler, 1993). For example, the maturational delays for cortically evoked potentials approximate the period of auditory deprivation prior to implantation (Ponton et al., 1996). Besides socio-psychological factors, the question of how electrical stimulation affects the auditory system, particularly auditory cortex, is therefore of increasing importance. To approach these problems, the use of animal models differing in the time of deafening and the onset and duration of stimulation can provide further insights.

1.1. Two-dimensional activity maps of cochleotopy in primary auditory cortex (AI)

It is a key feature of early sensory cortical areas that they contain complete and systematic representations of the sensory epithelium. Although the sensory epithelium of the auditory system is one-dimensional, the topographic representation of the receptor surface occupies two spatial dimensions in primary AI. Extensive electrophysiological mapping studies using multiple microelectrode penetrations showed that maps of the cat primary AI are characterized by neurons sensitive to different frequencies, resulting in a cochleotopic representation along the caudal/rostral dimension of AI (Merzenich et al., 1975). While the representation of single tones within the framework of cortical maps is fairly well understood, little is known about the nature and the degree of the topographic aspects of the representation of cochlear stimulation within cortical maps (cf. Dinse et al., 1997a; Raggio and Schreiner, 1999).

1.2. Optical imaging of intrinsic signals

Based on the close correlation between oxygen consumption and neural activity, new methods were developed to record optically from the exposed cortex in order to obtain two-dimensional reflectance changes. These changes were shown to correspond closely to the spatial distributions of the underlying neuronal maps (Malonek et al., 1997). Optical imaging has the advantage that it allows repeated and multiple measurements of functional maps following sensory stimulation in the same individual, with a spatial resolution of up to 50 μm (Frostig et al., 1990), revealing the contribution of distributed populations of cortical neurons including their subthreshold activity.

1.3. Towards a learning-based approach of electrical cochlear implant stimulation

Here we summarize our recent studies, in which we used optical imaging of intrinsic signals to map cortical representational areas evoked by electrical cochlear implant (CI) stimulation (Dinse et al., 1997b, 1998; Reuter et al., 1997). Our interpretation of the efficacy of CI-stimulation is largely focused upon the adaptive capabilities of the auditory system to re-interpret the new activity patterns, i.e. we do not assume that the beneficial effects are brought about by meticulously imitating electrically the pattern of activity normally present in an intact auditory periphery. In contrast, such a learning-based approach towards the understanding of CI-stimulation in both children and adults accounts for the intensive training required to obtain optimal results. In fact, during recent years, the functional relevance of experience-dependent cortical plasticity has been convincingly demonstrated. We therefore hypothesized that such processes may also be crucially involved in mediating the beneficial effects observed after chronic CI simulation.

1.4. Synopsis

In the following we briefly discuss some general aspects of cortical plasticity before recapitulating evidence for plastic reorganizational processes in the auditory system with particular emphasis on adult, post-ontogenetic plasticity. We then summarize our experimental findings of auditory cortex reorganization assessed with optical imaging of

intrinsic signals after chronic CI stimulation. We discuss the findings in the framework of plastic processes and suggest a hypothesis according to which the beneficial effects of CI stimulation rely on a re-learning of input patterns arising from an artificial sensory input via electrical stimulation.

2. General aspects of cortical plasticity

Heritable features acquired during evolutional time spans are of ultimate advantage for survival and are without exception structurally fixed. However, to cope successfully with the changes of environmental conditions occurring constantly during the lifespan of individuals, additional mechanisms are required that are not specified or limited by genetic constraints. In contrast to developmental plasticity, adaptation of adult brains does not rely on maturational and growth processes. Specifically, for learning-induced alterations the crucial role of so-called functional plasticity based on rapid and reversible modifications of synaptic efficacy is well-established. There is also agreement that plastic-adaptive capacities of various forms represent a general and ubiquitous cortical feature in fact present in all primary sensory and motor cortical areas.

2.1. Driving forces that lead to plastic changes

We assume a dynamically maintained steady state of representations that emerge during development and adulthood from maturational and learning processes reflecting the history of adaptation to a 'mean environment', i.e. the behaviorally relevant environmental history. Mean environment is defined as the accumulated and idiosyncratic experience of an individual. Adaptational processes are assumed to operate on these representations, and long-lasting changes are likely to occur when sensory input patterns are altered such that they deviate from the mean environment. A prominent example is the altered tactile input for the reading hand in Braille readers.

(a) The average steady state can be altered by changing the input statistics. Particularly effective are simultaneity, extensive repetitions, or more generally, spatio-temporal proximity in the parameter distribution of the input. Plastic changes induced in this way occur without involving attention or reinforcement. They define a class of non-cognitive adaptations that are largely based on bottom-up processing because of the driving nature of the input statistics.
(b) Attention can be drawn to a stimulus, thereby selecting it from others. Furthermore, the relevance can change depending on context, history and behavioral task, thereby modifying the processing of physically defined attributes. Modification of early sensory processing by attention and stimulus relevance reflects top–down influences.
(c) Reinforcement by reward or punishment usually accelerates adaptational processes. Such influences are assumed to be mediated by specific brain regions modifying early sensory processing.

2.2. The Hebbian metaphor

A central paradigm in the description and analysis of cortical plasticity is built around the Hebbian concept (Hebb, 1949), which states that episodes of high temporal correlation between pre- and post-synaptic activity are a pre-requisite for inducing changes in synaptic efficacy. Historically, this idea can be traced back to the 19th century (cf. James, 1890). In fact, since Hebb, the aspect of simultaneity of specific input parameter constellations has become a metaphor in neural plasticity, although the exact role of Hebbian mechanisms in use-dependent plasticity remains controversial (Cruikshank and Weinberger, 1996; Edeline, 1996). It has been suggested that the definition of Hebbian mechanisms must be extended beyond 'simultaneity' in the sense of strict coincidence to cover all temporal patterns arising from learning processes.

2.3. Use-dependent plasticity as a basis of perceptual and motor skills

One of the striking features of use-dependent plasticity is the correlation of cortical changes with performance (Recanzone, 2000). Perceptual

learning describes the ability to improve perceptual performance by training and practice, largely independent from conscious experience (cf. Gibson, 1953). Perceptual learning is usually characterized by a high specificity to the locality and the parameters of a stimulus, with little generalization, implying that the underlying neural changes occur most probably within early cortical representations that contain well-ordered topographic maps that allow high selectivity, but where generalization has not yet occurred. There is increasing evidence that changes in early cortical areas might be more directly linked to perceptual learning than previously thought (Fahle and Poggio, 2002).

More generally, the acquisition of skills has often been used as an index for the build-up of implicit memories. It has therefore been speculated that use-dependent plasticity might be strongly related to, if not a substrate for, implicit memory function.

2.4. Lesion- versus training-induced cortical plasticity

Lesion-induced plasticity includes the reorganization after injury and lesion, either induced centrally or at the periphery. This type of plasticity refers to aspects of compensation and repair of functions that had been acquired prior to injury or lesion. On the other hand, training- and learning-induced reorganization is often denoted as 'use-dependent plasticity' and describes plastic changes parallel to the behavioral improvement of performance, i.e. the acquisition of perceptual and motor skills (for reviews, in part with a particular emphasis on the auditory system, see King and Moore, 1991; Scheich, 1991; Scheich et al., 1993; Weinberger, 1995; Cruikshank and Weinberger, 1996; Edeline, 1996; Buonomano and Merzenich, 1998; Rauschecker, 1999; Recanzone, 2000; Dinse and Merzenich, 2002; Dinse and Böhmer, 2002).

3. Plasticity of cortical maps and receptive fields

3.1. Lesion-induced plasticity in adults

Large-scale reorganization in adults has first been described following digit amputation or deafferentation in the primary somatosensory cortex (Kelahan et al., 1981; Rasmusson, 1982; Merzenich et al., 1984). The main result was that the cortical area representing the skin surface removed by amputation or deafferentation did not remain silent, but was activated by stimulation of bordering skin sites. These early data indicated that sensory cortical representations in adults were not hard-wired, but retain a self-organizing capacity operational throughout life (Merzenich et al., 1984).

A series of lesion experiments performed in the adult auditory system in a variety of mammals confirmed the tremendous cortical reorganizational capacities. Months after a restricted unilateral lesion of the cochlea had been produced, the area of contralateral auditory cortex was partly occupied by an expanded representation of sound frequencies adjacent to the lesioned frequencies (Robertson and Irvine, 1989). Recently, a loss of surround inhibition and an unmasking of new excitatory as well as inhibitory inputs as a consequence of receptor organ damage has been demonstrated (Rajan, 2001). Interestingly, no comparable signs of plastic changes of the frequency map in the dorsal cochlear nucleus of adult cats following unilateral partial cochlear lesions have been found (Rajan and Irvine, 1998). However, in somatosensory system, large-scale amputations have been shown to involve sprouting and outgrowth of afferent connections (Florence et al., 1998). It remains to be seen if in the auditory system similar findings hold for comparable large-scale cochlear lesions.

3.2. Lesion-induced plasticity during development

There are many studies exploring the consequences of neonatal hearing loss and cochlear lesions on the central, specifically cortical auditory system (for reviews see Moore et al., 1993). For example, massive reorganization of frequency representations has been described in the midbrain and AI of chinchilla and cats after amikacin-induced basal lesions in the cochlea. Most striking was the presence of large regions in which all neurons had similar tuning properties (Harrison et al., 1991). Anatomical studies indicated that

there was no divergent thalamocortical projection indicative of an abnormal spread of the thalamocortical afferents across the frequency domain in AI (Stanton and Harrison, 2000). It was suggested that similar abnormal patterns of frequency representation will exist in human subjects with long-term neonatal hearing loss.

Abnormal cochleotopic organization in the auditory cortex has also been observed in cats exposed for three months to a frequency-modulated 8 kHz signal. Frequency maps measured in these cats as adults were characterized by a significant expansion of the frequency range the kitten had been stimulated with (Stanton and Harrison, 1996).

3.3. Training- and learning-induced use-dependent reorganization

As perceptual skills improve with training (cf. Gibson, 1953), a key question in cortical plasticity is how reorganizations are linked to parallel changes of perceptual performance. Monkeys trained for several weeks to discriminate the frequency of sequentially presented tones revealed a progressive improvement in performance (Recanzone et al., 1993). Electrophysiological mapping experiments performed at the end of the training revealed that the cortical representation, the sharpness of tuning, and the latency of the responses were greater for the behaviorally relevant frequencies of trained monkeys. Notably, the cortical area of representation was the only studied parameter that was correlated with behavioral performance. These results demonstrated that a long-term training protocol can modify the tonotopic organization of Al in the adult primate, and that this alteration was correlated with changes in perceptual acuity (Recanzone et al., 1993).

The framework of "modified use" as a determinant of cortical organization has been applied in a large number of investigations, mostly performed in somatosensory cortex (cf. Recanzone, 2000; Dinse and Merzenich, 2002). In this approach, plastic changes are evoked under rather natural conditions. For example, the implications of an episodic differential use following nursing behavior, as occurs during the normal life-span of an animal, have been shown in a study of lactating rats: The SI representation of the ventral trunk skin was significantly larger than in matched postpartum non-lactating or virgin controls (Xerri et al., 1994). However, while for studies of somatosensory plasticity the aspect of "use" and "no-use" provides a key feature that allows an easy and intuitive classification of plastic changes, it is quite possible that aspects of "practicing" or aspects related to the properties of input probabilities might be more appropriate concepts for the auditory domain (see also Dinse and Böhmer, 2002).

3.4. Human studies of cortical plasticity

The recent development of non-invasive imaging techniques has made it possible to study the impact of modified use and practice in humans. For example, in the somatosensory cortex of string players (Elbert et al., 1995), selective enlargement of that cortical territory was found that represented the fingering digits, which are engaged in a significantly higher amount of practice than in non-musician controls. In highly skilled, professional musicians, functional magnetic source imaging revealed an enlargement of dipole moments for piano tones as compared to non-musician controls, but not for pure tones of similar fundamental frequency. These changes were correlated with the age at which musicians began to practice (Pantev et al., 1998). Reminiscent of reorganization after frequency discrimination training in monkeys (Recanzone et al., 1993), human subjects have been reported to show plastic reorganization in the AI induced by frequency discrimination training over several weeks (Menning et al., 2000). Taken together, these studies suggest that even small alterations in practice enforced by the special demands of everyday life alter early cortical representations rapidly and reversibly.

3.5. The role of input statistics

Human studies are extremely beneficial in revealing signatures of cortical plasticity under daily routines. However, what are the factors that drive plasticity? In the case of skilled musicians,

potential candidates are the rate of occurrence of tones played or heard, the spectro-temporal patterns of sound, the level of attention, and the duration and frequency of practice. In fact, many lines of evidence indicate that variations of input statistics alone are sufficient to induce reorganization of cortical maps, without training, attention or reinforcement.

3.5.1. Intracortical microstimulation

Intracortical microstimulation (ICMS) has frequently been utilized to study reorganization in motor, somatosensory, auditory and visual cortices as well as thalamic relay nuclei (for a detailed account of ICMS-plasticity see Dinse et al., 1997c; Dinse and Merzenich, 2002). ICMS makes it possible to investigate locally the properties of functional plasticity, independent of the peripheral and subcortical pathways and independent of the constraints provided by particularities of a sensory pathway and its pre-processing. In a typical ICMS experiment, repetitive electrical pulse trains of very low currents are delivered via a microelectrode. The resulting synchronized discharges are assumed to drive plastic changes. The short time scale and reversibility of ICMS-effects support the hypothesis of modulations of synaptic efficiency.

In AI, ICMS induced fast changes in the tonotopic map and in the receptive field properties of cells. There was an enlargement of the cortical domain tuned to the acoustic frequency that had been represented at the ICMS site (Maldonado and Gerstein, 1996a,b; Chowdhury and Suga, 2000). In addition, synchronous oscillatory firing patterns of cortical neurons were enhanced after ICMS in a manner dependent on the anatomical distance between the two neurons (Maldonado and Gerstein, 1996b), supporting the view that neural cooperativity is subject to modification during reorganizational processes.

From a general point of view, the results obtained with ICMS demonstrate the capacity for cortical plasticity in the absence of peripheral stimulation.

3.5.2. Conditioning experiments

A specific type of associative learning, namely classical conditioning, has been studied for decades in the AI (Diamond and Weinberger, 1986; Gonzalez-Lima and Agudo, 1990; Weinberger et al., 1990; Scheich et al., 1993; Weinberger, 1995). Using a classical conditioning protocol, a tone of a given frequency (the CS +) was paired with an aversive electrical shock. Tuning curves recorded in AI before and after conditioning revealed a shift in the best frequencies in the direction of the frequency of the CS +; these shifts lasted up to a few weeks and could be reversed by extinction training. In another approach, the effect of a single neuron on another was evaluated by cross-correlation analysis of neuron responses recorded simultaneously in the AI of behaving monkeys (Ahissar et al., 1992). During the conditioning period there was a development of correlated activity for both the condition contingency and behavior and the condition contingency alone. Interestingly, persistent changes in functional connectivity required the establishment of the condition contingency together with behavior.

3.6. Pharmacological modulation of adult plasticity

The major source of cholinergic inputs implicated in learning and memory comes from neurons within the basal forebrain, which receives inputs from limbic and paralimbic structures. These inputs have been assumed to represent one example of a top–down system providing modulatory information of higher order processes. In animal experiments, pairing of sensory stimulation with electrical stimulation of the nucleus basalis results in rapid and selective reorganization (Edeline et al., 1994; Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998a). On the other hand, lesion of the cholinergic system has been shown to prevent plastic reorganization (Baskerville et al., 1997).

3.7. Plasticity of temporal processing

Most of what we know about cortical reorganization is largely based on the analysis of receptive fields and on the areal extent of representational maps. On the other hand, temporal processing, i.e. the computation of sequential events, is still poorly understood. Under natural

conditions, stimuli never appear in isolation. Therefore, timing and sequencing impose severe temporal constraints that modulate neuron responses. This appears particularly crucial for the auditory domain (McKenna et al., 1989; Merzenich et al., 1993; Schreiner et al., 1997; Brosch et al., 1999), but significant effects of sequencing are also found for visual and somatosensory systems.

So far, there have been only a few studies exploring the plastic capacities of temporal processing. For example, to test whether experience can modify the maximum following rate of neurons of AI of adult rats, trains of brief tones with random carrier frequency but fixed repetition rate were paired with electrical stimulation of the nucleus basalis. Dependent on the frequency of basalis stimulation, pairing induced an extensive cortical remodeling of temporal response properties (Kilgard and Merzenich, 1998b).

3.8. Subcortical plasticity

Studies of subcortical and brainstem structures have clearly shown that reorganizational changes occur along the entire sensory pathway. As most of the experiments have been performed in non-auditory systems (for auditory midbrain studies see Harrison et al., 1993; Yan and Suga, 1998), no details are given here (cf. Dinse and Merzenich, 2002). The emerging picture emphasis that much of the plasticity encountered at a subcortical level may depend on feedback connections from the cortex (Yan and Suga, 1998; Kaas, 1999). It was also suggested that the usually extensive cortical reorganizations may in part depend on activation of the widespread horizontally connected network, which is lacking in thalamic nuclei.

3.9. Maladaptive consequences of cortical plasticity

The final outcome of reorganizational processes may not necessarily be beneficial. There is increasing evidence that abnormal perceptual experiences such as the phantom limb sensation arise from reorganizational changes induced by the amputation of the limb. Consequently, a number of perceptual correlates of cortical reorganization have been described, such as a precise topographic mapping of the phantom onto the face area (Ramachandran et al., 1992). People with amputations often have the feeling that the amputated limb is still present (phantom limb sensation). Subjective tinnitus, the hearing of a disturbing tone or noise in the absence of a real sound source, shares many similarities with the sensation of phantom limb experienced by many amputees. Therefore, tinnitus has been thought of as an auditory phantom phenomenon (Jastreboff, 1990; Rauschecker, 1999). Studies using 2-deoxyglucose autoradiography in gerbils treated with salicylate, which is known to generate tinnitus, demonstrated increased activation in areas of the AI (Wallhäusser-Franke et al., 1996). Using magnetic source imaging on subjects suffering from tinnitus, a marked shift of the cortical representation of the tinnitus frequency into an area adjacent to the expected tonotopic location was observed. There was a strong positive correlation between the subjective strength of the tinnitus and the amount of cortical reorganization, indicating that tinnitus is related to plastic alterations in AI (Mühlnickel et al., 1998).

Some forms of dysfunctions in normal phonological processing, which is critical to the development of oral and written language, have been speculated to derive from initial difficulties in perceiving and producing basic sensory-motor information in rapid succession, emphasizing the crucial role of temporal parameters (Wright et al., 1997). Yet, there is controversy about the role of auditory temporal information processing in causing language impairments (Bishop et al., 1999). On the other hand, children with a particular type of language-based learning deficit, engaged in adaptive training of their temporal processing skills, showed a markedly improvement in their abilities to recognize brief and fast sequences of non-speech and speech stimuli, suggesting that the reorganizational changes are specifically sensitive to the temporal parameters of the input (Tallal et al., 1993; Merzenich et al., 1996). Taken together, the maladaptive consequences of auditory cortical plasticity are more and more acknowledged as a major factor in various forms of dysfunction.

3.10. Summary

Generally, massive and enduring reorganizations have been described for primary AI, confirming the contemporary view that all cortical areas are modifiable beyond the critical sensitive periods during development. The findings summarized demonstrate impressively that the sensorimotor, and particularly the auditory cortical representations in adults, are not hard-wired, but retain a self-organizing capacity operational throughout life.

4. Beneficial effects of long-term cochlear stimulation: signature of cortical, use-dependent plasticity

4.1. Baseline studies: optical imaging of the effects of electrical CI stimulation in normal adult cats

We have previously shown that mapping of reflectance changes (optical imaging of so-called intrinsic signals) in primary AI, associated with stimulation by selected electrodes of a multichannel device implanted in the cochlea of acutely deafened cats, revealed details about the underlying topography of the frequency representations (Dinse et al., 1997a). As illustrated in Fig. 1 for an acutely deafened cat, CI-stimulation evoked topographically restricted areas of reflectance changes indicative of enhanced neural activity. Stimulation from electrode pairs representing increasingly higher frequency sites, shifted activity from caudal to rostral (for a discussion of frequency sites involved see below). These shifts are consistent with the normal frequency organization in AI (Merzenich et al., 1975), supporting the cochleotopic nature of CI stimulation.

To analyze the cochleotopic selectivity more closely, we computed so-called composite maps, which allow visualization of the specificity of the cortical activity maps for a given electrode pair. The presence of a normal cochleotopic gradient is indicated by a systematic shift of compact regions of activity from approximately caudal to rostral upon stimulation of increasingly higher frequency sites.

As a further measure of cortical map organization, we calculated the overlap of the cortical activation patterns observed with stimulation of two adjacent electrode pairs, as well as the total activation overlap evoked by all stimulated sites. Depending on the degree of orderliness within a cochleotopic map, stimulation of adjacent cochlear positions produces an overlap of cortical activation. In the case of a well-ordered cochleotopy, small areas of overlap will result (Figs. 1–3). In contrast, highly overlapping activation due to coactivation of identical cortical zones indicates a lack of well-ordered representational selectivity. The amount of overlap present in the adult controls (Figs. 1 and 2) can also be found in normal animals following acoustic stimulation with pure tones (Bakin et al., 1996; Hess and Scheich, 1996; Harrison et al., 1998; Dinse et al., 2000; Spitzer et al., 2001); for a general discussion of overlap of cortical maps see (Godde et al., 1995).

To provide an estimate of the "effective" frequency range stimulated by the electrodes, we made use of average data on the length of the scala tympani and the corresponding frequency sites (Schuknecht, 1960; Hatsushika et al., 1990). Based on their data, prominent reflectance changes are most likely to occur in the high-frequency representation of AI assuming an overall length of the inserted electrode portion of about 6 mm, the frequency range most probably stimulated is between 6 and about 40 kHz. By the same token, assuming roughly 2 mm distances between the electrode pairs, the electrode pairs are presumably separated in the frequency domain by about one octave.

4.2. Effects of acoustic deprivation: optical imaging of CI stimulation in neonatally deafened cats

Imaging data from neonatally deafened cats after 6–24 months of acoustic deprivation differed in every aspect from those obtained in adult controls. For example, stimulation currents required to obtain reliable responses were on average twice those needed for normal adults. Cochleotopic maps recorded in neonatally deafened animals showed remarkable variability: maps were characterized

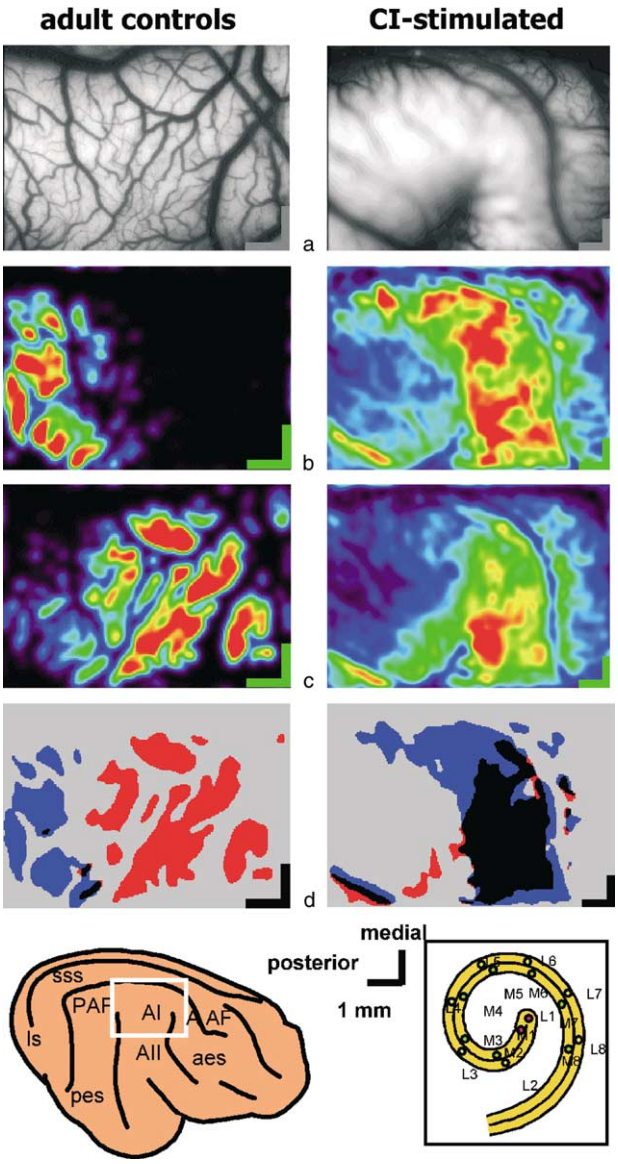

Fig. 1. Spatial distribution of reflectance changes of optically recorded intrinsic signals corresponding to neural activity maps recorded in cat AI in response to CI stimulation. Warm colors show regions of maximal reflectance changes, indicating enhanced cortical activation. Each single condition map was individually scaled to its maximal values. Scale bar is 1 mm. Posterior is left, medial up. (a) Image of the exposed brain surface. Location used for optical imaging (white frame) is indicated in the schematic drawing of a cat brain to illustrate the layout and parcellation of cat auditory cortical fields (bottom). AAF—anterior auditory field; AI—primary auditory cortex; AII—secondary auditory field; PAF—posterior auditory field, sss—suprasylvian sulcus; 1s—lateral sulcus; aes—anterior ectosylvian sulcus; pes—posterior ectosylvian sulcus. Left column: Examples from an adult cat with normal hearing experience that was implanted directly prior to the imaging experiment. Electrical stimulation of electrode pairs 11-1m (b) and 21-2m (c) with 600 μA. The full color scale corresponds to fractional reflectance changes of 0.9% and 0.8%. Right column: Examples from an adult cat that was neonatally deafened and imaged after three months of CI-stimulation. Electrical stimulation of electrode pairs 11-1m (b) and 21-2m (c) with 50 μA. The full color scale corresponds to fractional reflectance changes of 5.4% and 2.4%. (d) Composite maps calculated from the single condition maps shown in (b) and (c) displaying selectivity for a preferred electrode pair, which is color-coded (blue indicating electrodes 11-1m, red indicating electrodes 21-2m). Black marks overlap. The computation was performed for activation at the 50% level of maximal signal amplitude. Bottom right shows a schematic drawing of the multichannel electrode indicating the electrode sites being stimulated (11-1m in (b), and 21-2m in (c)).

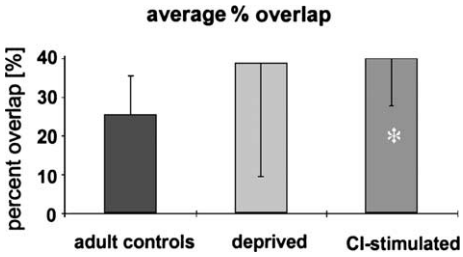

Fig. 2. Average percentage overlap for adjacent electrode pairs expressed as the quotient of overlap area and total activated area for the three experimental groups.

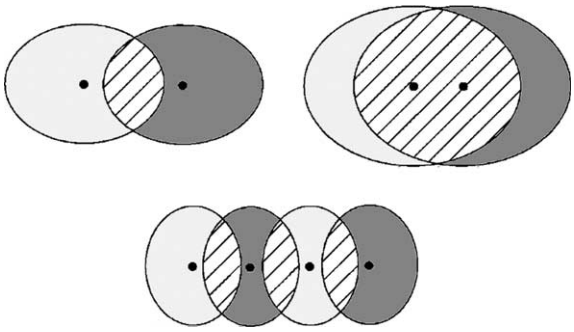

Fig. 3. Schematic illustration of the type of cortical topography observed in the three experimental groups. Shown are two activation patterns (light and dark grey) as evoked by two neighboring electrode sites, together with the overlap between them (hatched area) and the centers of the respective activity maps. Top left: normal adult cats; top right: CI stimulated animals; bottom: neonatally deafened animals. Depending on the degree of order within a cochleotopic map, stimulation of adjacent cochlear positions results in a given overlap of cortical activation. In the case of a well-ordered cochleotopy, small areas of overlap will result (top left). In contrast, highly overlapping activation due to coactivation of identical cortical zones indicates a lack of well-ordered representational selectivity (top right). The net-increase of overlap seen in the acoustically deprived animals (bottom), results from the emergence of isolated islands of activity, indicating a disintegration of the normally compact representational maps of normal adult cats.

by irregular zones of activity making them diffuse and patchy.

This observation was confirmed by inspection of the composite maps: regions selective for a given electrode site could be repeatedly represented. Activated areas could appear as small islands surrounded by areas with different tuning for electrode selectivity, indicating severe distortions of the cochleotopic map. As a result, the nature of overlap was also different. Due to the patchiness, we typically found many areas of overlap of varying size. However, as a net effect, the total area of overlap was increased (Fig. 3). Quantitative analysis revealed that the overlap distribution was much broader with a large number of cases having a very high percentage of overlap (Fig. 2).

From this we concluded that, in addition to a decrease in sensitivity, impairment of the cochleotopy is one of the consequences of the neonatal deafening. This type of reduction of cochleotopy is mainly due to the emergence of isolated islands of activity (Fig. 3), which indicates a disintegration of the normally compact representational maps of normal adult cats (cf. Wiemer et al., 2000). However, although cortical maps in acoustically deprived animals were severely altered, it is noteworthy that despite the lack of acoustic sensations over several months, cortical representations still could be activated.

4.3. Effects of chronic CI-stimulation in neonatally deafened cats

To demonstrate the positive impact of chronic electrical stimulation during development on AI, a group of neonatally deafened animals was electrically stimulated. CI-stimulation was performed for a period of three months, using the 'continuous interleaved sampling' (CIS) strategy, in which all electrodes were stimulated near-simultaneously within 1 ms at high rates (Wilson et al., 1991; cf. Fig. 4). Electrical stimulation was driven by the acoustic environment of the animals. When stimulated, animals showed pinna movements as well as head and body orienting behavior indicating that the electrical stimulation of the cochlea evoked behaviorally relevant sensations. In the context of our findings it is important to note that, in human patients, the use of the CIS stimulation strategy is highly effective in providing open-set speech recognition (Wilson et al., 1991, 1995).

After the three-month period of chronic CI stimulation, cortical organization was assessed

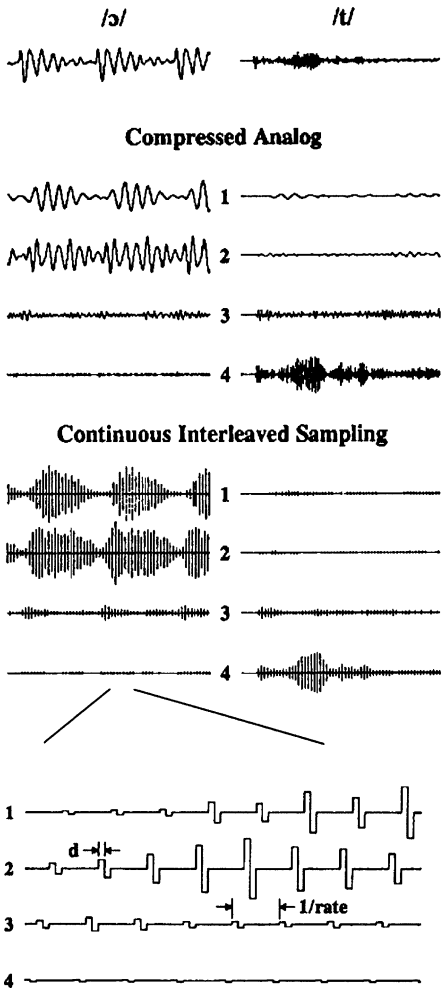

Fig. 4. Waveforms produced by simplified implementations of the *compressed analog* and the CIS strategies. Top: different types of speech inputs. Middle: Stimulus waveforms for CA and CIS processors. The duration of each trace is 25.4 ms. Channel numbers are given. For comparison, only four channels are shown. The pulse amplitudes reflect the envelope of the band-pass output for each channel. In actual implementations, the range of pulse amplitudes is compressed using a logarithmic or power-law transformation of the envelope signal. Bottom: Expanded display of the CIS waveform. Pulse duration per phase (*d*) and the period between pulses (1/rate) are indicated. The total duration of each trace is 3.3 ms. (Reprinted with permission from (Wilson et al., 1991).)

by means of optical imaging. The results revealed broad, multi-peaked but well-defined zones of enhanced activity covering nearly the entire AI (Fig. 1). Compared to normal controls, animals of this group were characterized by a several-fold reduction in current necessary to drive cortical maps. In addition, despite the low currents, the amount of cortical activation following single electrode stimulation was enhanced. This finding was corroborated by calculating the integrated activity of the optical imaging maps, which was about 50% higher than for normal adults.

Another typical feature of the CI stimulated group consisted of a substantial reorganization of the cochleotopic maps. As illustrated in the single condition and the composite maps, regions selective for a given electrode site could comprise large cortical territories (Fig. 1).

While in normal adults, the overlap between cortical activations evoked by neighboring electrodes was fairly small, in the CI stimulated animals large cortical regions responded equally well to both electrodes, indicating a profound reduction of representational selectivity. As a result, the zones of overlap were also significantly enlarged (Figs. 2 and 3).

While the reduction in cochleotopy in unstimulated animals could be explained in terms of disintegration of the cortical maps, changes of cochleotopy in CI stimulated animals appeared to be largely due to an integration of inputs over large cortical territories, supporting the notion that different mechanisms are involved in mediating the reduction of topographic representations observed in neonatally CI stimulated and unstimulated animals (Fig. 3).

4.4. Summary of main findings

Our data indicate a substantial reorganization of auditory cortical maps after chronic CI-stimulation (Dinse et al., 1997b, 1998; Reuter et al., 1997). The most important finding were that a three-month period of chronic stimulation did not re-installed the "status" typically found in normal adults, but instead resulted in the emergence of an entirely "new" topographical and physiological organization.

In fact, all parameters analyzed were different:

Parameter studied after CI stimulation	Compared to normal adults	Compared to deprived animals
Intrinsic signal strength	Enhanced	Enhanced
Sensitivity	Enhanced	Enhanced
Integrated activity	Enhanced	Enhanced
Cortical area	Enlarged	Enlarged
Cortical overlap	Enlarged	Comparable size, but different spatial pattern
Cochleotopy	Reduced	Comparable size, but different spatial pattern
Cell number	Slightly reduced[a]	Enhanced[a]

[a] According to Reuter et al. (1997).

On the other hand, when compared to the status of the acoustically deprived animals, CI-stimulation clearly had a restoring effect on cortical responses. The data demonstrate that chronic CI-stimulation in neonatally deafened animals not only counteracts the effects of deprivation, but goes beyond a restoration of the response properties found in normally reared animals.

A particularly interesting finding was the net effect of reduced cochleotopy in parallel with an enlarged overlap. We have argued above that in deprived animals the reduced topographic order resulted from a disintegration, in which a clear topography is lost because of the emergence of many small islands of representations. In contrast, in the CI-stimulated animals, the same net effect was due to an integration of input leading to large, "joint" representations containing the stimulated frequency sites of the cochlea (cf. Fig. 3).

4.5. Discussion and open questions

While there have been many studies focusing on the investigation of the discharge pattern of the auditory nerve, the cochlear nucleus or the auditory midbrain in response to CI stimulation (Hartmann et al., 1984; Brown et al., 1992; Snyder et al., 1990, 1991), there have been only few studies addressing the question of properties of cortical responses after CI stimulation. In adult animals that were implanted directly prior to electrophysiological recordings, cortical response behavior following CI-stimulation was reported to be largely identical to that induced by acoustic stimulation (Raggio and Schreiner, 1994; Schreiner and Raggio, 1996). In congenitally deaf cats, several weeks of CI-stimulation of large portions of the cochlea resulted in recruitment of the AI as indicated by maturation of synaptic transmission (Klinke et al., 1999). Major differences in cortical response distributions on the ectosylvian gyrus of adult cats due to deafening have been observed in long-term deafened animals (Raggio and Schreiner, 1999). Recent imaging data obtained in prelingually deaf patients before and after cochlear implantation, using positron emission tomography (PET), support the relevance of these animal findings for human patients (Lee et al., 2000). After cochlear implantation, these authors found a positive correlation between the size of the hypometabolic area and a hearing-capability score.

Accordingly, many lines of evidence indicate that the underlying plastic adaptational properties of cortical auditory neurons might provide an additional substrate involved in mediating the highly variable improvement of open speech understanding with practice often observed in patients using cochlear implants.

Yet, given the observation that children and adults implanted with multichannel electrodes and stimulated by a CIS strategy obtain a significant degree of open speech understanding, the question remains how this can be accomplished given the type of changes found in our cat experiments, assuming an analogy between human performance and our animal model.

5. The effective coding of CI-induced reorganizational changes

5.1. Proportionality of use and cortical changes

How are plastic changes coded? That is, what are the neural changes that lead to behavioral or perceptual changes? There appears to hold one simple rule of thumb: extensive use or practicing leads to enlarged cortical territories, while limited use or no-use results in a reduction in the size of cortical representation, indicating a form of proportionality between representational area and use (Recanzone, 2000; Dinse and Merzenich, 2002). Representational size correlates with the number of neurons activated by a given task or stimulation. This view implies that enhanced performance developing in parallel to plastic changes is at least partially achieved by recruitment of processing resources.

Here we argue that the effects of chronic CI-stimulation capture the typical signature of use-dependent plasticity, i.e. the development of an enlarged, common joint representation of all stimulated frequency sites that gives rise to a loss of distinct cochleotopy.

In this scenario, the increase in performance, i.e. the re-gained or gained speech understanding capability, is due to the development of enlarged representations, which translates into a recruitment of the number of neurons involved in processing certain stimulus features, thereby increasing the power of processing. It should be noted that comparable reorganizational effects have been observed in cats deafened as adults, suggesting that comparable mechanisms are effective in driving post-ontogenetic reorganization, where maturational aspects play no role (Dinse et al., 1997b, 1998).

In the following we briefly discuss whether there is evidence supporting such an hypothesis, and what are the potential driving forces leading to these particular changes.

5.2. Coding of perceptual improvement

Experimental evidence exists from studies of somatosensory cortex that plastic changes of the type described after CI-stimulation, in particular enlarged representation of high overlap, can be instrumental in providing enhanced discrimination performance. In order to test directly the potential role of sensory input statistics for the induction of cortical plasticity without involving cognitive factors such as attention, we introduced a coactivation protocol: synchronous neural activity, necessary to drive plastic changes, was generated by the simultaneous, associative pairing of tactile stimuli. A few hours of coactivation resulted in selective and reversible reorganization of receptive fields and cortical maps in somatosensory cortex of adult rats characterized by the emergence of a large joint representation of the two stimulated skin sites (Godde et al., 1996). In humans, a few hours of coactivation induced a discrimination improvement as indicated by a lowering of the spatial 2-point discrimination threshold (Godde et al., 2000). A combined assessment of discrimination thresholds and recording of somatosensory evoked potentials in human subjects revealed that the individual gain of discrimination performance was correlated with the amount of cortical reorganization, as inferred from the shifts of the location of the N20 dipole localized in SI (Pleger et al., 2001). Combined, there is in fact evidence that variation of input statistics alone can lead to improved discrimination performance, which at a cortical level, is paralleled by an enlargement of cortical representational maps.

More generally, the discrepancy between perceptual thresholds and single neuron properties is not a new finding. For example, hyperacuity cannot be explained based on concepts of receptive field sizes of single cells (Westheimer, 1979). From a theoretical point of view, the 'coarse coding' principle (Baldi and Heiligenberg, 1988) has been used to explain high resolution performance by a population of neurons with broad tuning characteristics: given sufficient overlap between tuning curves, any desired resolution can be achieved. The coarse coding principle is a variant of the more general population coding approach assuming that it is not the property of a single cell that determines behavior, but instead large ensembles of neurons. For example, in somatosensory cortex,

small ensembles of 30–40 broadly tuned neurons were able to identify the location of a single tactile stimulus on a single trial basis (Nicolelis et al., 1998; Ghazanfar et al., 2000).

In addition, temporal aspects of processing, which were not addressed in the framework of the optical imaging experiments, are an additional, but highly significant candidate code. Conceivably, changes in temporal coding are similarly important for an understanding and interpretation of cortical plasticity (for an extended discussion of the problem of coding of plastic changes see Dinse and Merzenich, 2002).

5.3. The role of timing: the particular implication of using the continuous interleaved sampling stimulation strategy

Above, we have stressed the importance of the Hebbian metaphor, according to which simultaneity and extensive repetitions play a major role in mediating reorganization. In order to explain the specific changes evoked by chronic CI-stimulation, one has to consider the particular type of stimulation strategy. This is where the continuous interleaved sampling strategy comes in.

A key feature of the *continuous interleaved sampling* strategy is its high rate of stimulation on each channel using brief pulses and minimal delays, so that rapid variations in speech can be tracked faithfully. Accordingly, this strategy activates all available electrode channels within <1 ms in a frequency-specific weighted-manner (Fig. 4). Given the time constants of cortical neurons, a jitter in the range of a millisecond can, at a cortical level, be assumed to be interpreted as full simultaneity. In addition, quasi-simultaneous activation of all channels is performed at extremely high repetition rates >1000 Hz (Wilson et al., 1991). The long-term exposure to such a form of stimulation that is entirely different from any normal type of input, fulfills all requirements for induction of plastic changes. In particular, the inherent aspect of simultaneity predicts the manifestation of a large, cortical territory representing all stimulated electrode sites, which is exactly what we observed.

There are a number of predictions that can be tested experimentally. First, utilizing the new non-invasive imaging techniques should reveal comparable cortical reorganization in humans subjected to the continuous interleaved sampling strategy. On the other hand, the use of stimulation strategies qualitatively different from the particular properties of the continuous interleaved sampling strategy should result in predictable differences in cortical reorganization. For example, strategies not relying on such a high degree of simultaneity should not show the dramatic increase of overlap between cortical maps. In addition, introducing attentional aspects as well as meaning and perceptual relevance should lead to systematic deviations of the nature of plastic changes.

6. Outlook

We hypothesize that electrical stimulation of auditory nerve fibers during development has a beneficial effect on maturation, thereby preserving cell numbers to some extent (Reuter et al., 1997). However, recent histological examination of the spiral ganglion cells following neonatal deafness combined with long-term CI-stimulation revealed no more than a 50% cell survival (Leake et al., 1999). Conceivably, a functional recovery can take place independent of the histological recovery, at least when a certain minimum requirement of cell numbers is exceeded. In fact, it has been argued that the number of cells required for good speech perception might be quite low (Blamey, 1997).

The specific timing aspects of the *continuous interleaved sampling strategy* has been speculated to play a crucial role in mediating the increase of cortical territory at the cost of an impaired topographical order, but for the benefit of a large joint representation. The latter enables a recruitment of processing resources due to cooperative processes within distributed populations of neurons. How far the enhanced sensitivity, i.e. reduced current thresholds, observed after CI-stimulation is also due to the particular timing of the stimulation strategy, or simply due to the electrical stimulation, remains to be clarified. We argue that all changes in concert help higher processing stages to learn how to interpret new activity patterns arriving from the periphery. In this view, electrical

implant stimulation does not rely on a perfect imitation of normal patterns of peripheral neural activity, but on a re-learning of input patterns arising from an artificial sensory input via electrical stimulation. In line with many current views, our data support the crucial aspect of learning and training as a central factor for the interpretation and understanding of the effects of electrical cochlear stimulation.

In conclusion, we suggest that the ability of gaining/re-gaining speech understanding mediated by CI-stimulation is accomplished by new strategies of cortical processing due to enhanced cooperativity among large populations of neurons that help higher processing stages in interpreting new patterns arriving from the periphery. These strategies are thought to emerge from adaptational capacities in response to the constraints imposed by the properties of the new input statistics that in turn result from the stimulation strategy employed.

Appendix A. Material and methods

A.1. General animal preparation

A total of 22 cats were used. For a detailed account of our methods see (Dinse et al., 1997a, 2000; Reuter et al., 1997). During imaging, the animals were continuously kept anaesthetized with barbiturate.

A.2. Deafening, electrode implantation and chronic stimulation

Adult animals were acutely deafened by intracochlear injection of neomycine sulfate in both ears. Neonatal deafening was performed by means of daily subcutaneous injection of neomycinsulphate over a period of 2–3 weeks in 12 cats. Deafness was assessed by recording auditory brainstem responses (ABRs) and by cochlear histology. All neonatally deafened animals were implanted at the age of 7 weeks with human multichannel electrodes (Cochlear Ltd. Australia or Advanced Bionics Corp. USA). Seven of these animals were not stimulated during a subsequent period of up to 24 months. Five animals were chronically stimulated 4 h per day, five days a week for a period of 3–4 months, with biphasic square pulses (75 μs/phase), delivered at 1666 Hz using the CIS strategy (Wilson et al., 1991). Electrical stimulation was driven by the acoustic environment and was processed using speech processors for filtering and compression (Advanced Bionics) and decoded by the implant receiver carried by the animals. Stimulus intensity was set to 2 dB-μA above EABR threshold. Electrode impedance was regularly checked and was in the range of 5–50 KΩ.

A.3. Stimulation during optical recording

For optical imaging, different pairs of electrode sites were stimulated with biphasic current pulses of 75 or 100 μs duration/phase. Minimal but suprathreshold stimulation currents were used to evoke reliable reflectance changes. Each trial consisted of six stimuli applied at repetition rates of 3 Hz. Each trial was repeated 6–12 times.

A.4. Optical recording

For optical measurements, we used a slow scan 12 and 14 bit digital CCD-camera. Averaging procedure was the same as described elsewhere (Godde et al., 1995; Dinse et al., 1997a, 2000). Each trial was separated by a pause of about 20 s. The cortex was illuminated with either a 546 or a 578 nm light source.

A.5. Computation of maps and data analysis

All images were computed by dividing or subtracting a non-stimulus condition from a stimulus condition (single condition map). The spatial distributions of reflectance changes were color-coded, black indicating no activation. To analyze cochleotopy by visualization of the preferred electrode sites, so-called composite maps were computed for three adjacent electrode-pairs based on the corresponding single condition maps. Quantitative analysis of overlap was obtained by calculating the percentage overlap areas for stimulation of adjacent electrode sites as the quotient of overlap area and total activated area. To provide a quantitative

description for the amount of cortical activation, integrated activity was calculated as the sum of the negative reflectance changes of each pixel for each image.

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