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Plastic Changes in the Central Auditory System After Hearing Loss, Restoration of Function, and During Learning

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Syka, Josef. Plastic Changes in the Central Auditory System After Hearing Loss, Restoration of Function, and During Learning. *Physiol Rev* 82: 601–636, 2002; 10.1152/physrev.00002.2002.—Traditionally the auditory system was considered a hard-wired sensory system; this view has been challenged in recent years in light of the plasticity of other sensory systems, particularly the visual and somatosensory systems. Practical experience in clinical audiology together with the use of prosthetic devices, such as cochlear implants, contributed significantly to the present view on the plasticity of the central auditory system, which was originally based on data obtained in animal experiments. The loss of auditory receptors, the hair cells, results in profound changes in the structure and function of the central auditory system, typically demonstrated by a reorganization of the projection maps in the auditory cortex. These plastic changes occur not only as a consequence of mechanical lesions of the cochlea or biochemical lesions of the hair cells by ototoxic drugs, but also as a consequence of the loss of hair cells in connection with aging or noise exposure. In light of the aging world population and the increasing amount of noise in the modern world, understanding the plasticity of the central auditory system has its practical consequences and urgency. In most of these situations, a common denominator of central plastic changes is a deterioration of inhibition in the subcortical auditory nuclei and the auditory cortex. In addition to the processes that are elicited by decreased or lost receptor function, the function of nerve cells in the adult central auditory system may dynamically change in the process of learning. A better understanding of the plastic changes in the central auditory system after sensory deafferentation, sensory stimulation, and learning may contribute significantly to improvement in the rehabilitation of damaged or lost auditory function and consequently to improved speech processing and production.

I. INTRODUCTION

The role of the auditory system in mammals is to inform the subject about the acoustical environment and about the presence of species-specific acoustical communication signals. In humans, the latter function is dominant since one of the specific features of humans is the ability to learn and use language. It is the loss of auditory

receptors in childhood, either inherited or acquired, that precludes the development of normal speech in a child, leaving the child deaf and dumb. Yet contemporary rehabilitation techniques, based on electronic devices such as hearing aids with robust amplification or, particularly, cochlear implants, are able to substitute for the missing receptors and, when initiated in early childhood, to guarantee quasi-natural language development. The rehabilitation of hearing function with cochlear implants is also possible in adults, especially when the period between the loss of hearing and the introduction of the cochlear implant is not too long. A limited ability to differentiate sounds with the aid of cochlear implants is also acquired in adults who were born deaf. These examples show that not only during childhood, but also in adulthood, the auditory system is plastic and may recover some of its basic functions.

Many plastic changes in the brain and in the receptor organs occur only in developing organisms as a continuation of embryological development, i.e., after birth (285). In humans, the activation of the auditory system, as indicated by the occurrence of acoustic brain stem reflexes, starts in the 26–28th gestational week, and the development of hearing function continues for several years. Similar precocial development of hearing function occurs in experimental animal models used in auditory research such as guinea pigs or chinchillas, whereas altricial development of hearing, i.e., with the start of hearing after birth, is known to be present in the mouse, rat, ferret, gerbil, and cat. In mammals, the loss of hearing receptors at an early postnatal age results in plastic changes in the central auditory system similarly like in the visual and somatosensory systems (118, 129, 273). In mammals, in contrast to other vertebrates, the hair cells in the cochlea do not regenerate and the plastic processes in the central auditory system may be different from other vertebrates; therefore, this review is limited to the plasticity occurring in the auditory system of mammals and does not cover the problems of plasticity in birds and other submammalian orders.

The physiology of hearing has been positively influenced by a related scientific discipline, psychoacoustics. Psychoacoustics has been defined as the study of the relationship between the physical properties of sound stimuli and the behavior this stimulation evokes (401). Detection, discrimination, identification, and scaling have been the primary measures of behavior studied by psychoacousticians. However, psychoacoustics by definition presupposes that the behavior is more or less steady and therefore does not expect that essential changes occur in the auditory system during the investigation. Yet several recent studies have demonstrated that if the stimulation has some informational meaning for the animal, the properties of receptive fields and maps in the central auditory system change, mainly at the cortical and thalamic level (366). Cortical and thalamic neurons may change their characteristic features in the process of learning and memory. Such plastic changes, together with plastic changes after partial and total hearing loss, serve as evidence for the dynamism and plasticity of the auditory system and against the traditional view of the auditory system as a hard-wired system where change is impossible.

The loss of hearing function may not necessarily be complete, but even a partial decline in the number of inner ear receptors results in a limitation of hearing function in humans, especially in the intelligibility of speech. The deterioration of hearing function, particularly at high frequencies, is a process that inevitably accompanies aging in humans as well as in other mammals (379). The dominant component of presbycusis is the gradual degeneration of hair cells mainly in the basal part of the cochlea; however, its central component is usually based on sclerotic processes in the brain. It is the aim of contemporary research to recognize the compensatory processes that exist in the adult auditory system with the aim of utilizing them for the rehabilitation of hearing function.

The auditory system, unlike other sensory systems, is in modern humans exposed to ever-increasing overstimulation. Noise exposure induces degenerative changes of the sensory receptors in the inner ear, with an obvious destruction of the outer hair cells at first. With continuing noise stimulation or with higher intensity noise, the loss of outer hair cells is followed by the loss of the inner hair cells. Ultimately, the postexposure changes in the inner ear are similar to those following mechanical lesions of the receptor organ, lesions induced by ototoxic drugs, such as aminoglycoside antibiotics, or degenerative changes occurring during aging (328). The changes in the central auditory system after any of these pathological states are to some extent similar; however, in the case of noise exposure, the plastic changes resulting from the loss of function of peripheral receptors are preceded by specific changes in the function of auditory neurons, elicited by overstimulation. Understanding the mechanisms of the changes in the auditory system occurring during and after noise exposure may be helpful in the prevention of this pathology and in its rational cure.

Many aspects of plasticity in the auditory system, both in the developmental period and during adulthood, are similar to the plasticity in other sensory systems and share similar mechanisms. It was the intention of the reviewer not to extend the scope of the review in this direction, since many excellent reviews exist covering the problems of plasticity in other sensory systems and the problem of plasticity in sensory systems in general, independent of the individual systems (75, 129, 273). For more detailed information about individual aspects of plastic changes in the auditory system, other recent reviews can be consulted (11, 113, 214, 240, 261, 274, 292, 328, 329, 379).

II. PLASTIC CHANGES IN THE AUDITORY SYSTEM AFTER TOTAL OR PARTIAL LESIONS OF THE INNER EAR

A. Effects of Complete Removal of the Inner Ear

1. Neonatal ablations

A common feature of sensory systems is a topographical projection from the sensory surface to various levels within the central nervous system. Thus retinotopic and somatotopic maps are internal representations of the retina and the body surface, respectively. In the auditory system, the sensory epithelium is rerepresented in all successive nuclei within the auditory pathway up to and including the auditory cortex. Because sound frequency is space mapped in the cochlea, the cochleotopic representation is usually named tonotopic representation. Numerous studies in recent years have shown that the central sensory maps are subject to reorganization as a result of manipulation of the peripheral sensory input particularly during early development. One of the first studies exploring the phenomenon of plasticity in the sensory systems was the pioneering studies by Hubel and Wiesel (108, 375, 376), who demonstrated changes to ocular dominant columns of striate cortex in monocularly deprived kittens. In the somatosensory system, a restricted peripheral deafferentation in developing animals results in the reorganization of subcortical and cortical somatotopic maps such that areas that would normally receive input from the denervated regions become used for the representation of the adjacent skin surface (130). In the auditory system, many of the studies of developmental neuroplasticity have focused on the effect of deafening on the immature auditory system. This work has shown that surgical removal of one cochlea in neonatal mammals results in a loss and shrinkage of neurons in the cochlear nucleus (92, 212, 346) and superior olivary complex (213, 247), in the formation of new connections between the cochlear nucleus on the intact side and various target structures in the brain stem (144, 286) and midbrain (234, 218, 215), and an increase in the responsiveness of inferior colliculus (142, 145, 217) and primary auditory cortex (276) neurons to acoustic stimulation of the ipsilateral, intact ear. In all of these experiments, altricial animal species were used, in which the development of hearing as well as other senses continues for some time after birth (cat, ferret, and gerbil).

In initial experiments with adult cats (276), it was shown that in cats reared with a neonatal cochlear ablation, the primary auditory cortex (AI) contralateral to the operated ear showed a normal tonotopic map derived from single neurons and neuronal clusters. The thresholds at many recording sites were as low as those observed in the AI ipsilateral to the operated ear. This was in marked contrast to the results of recordings in normal adult cats, in which only ~65% of AI neurons were excited by sound delivered to the ipsilateral ear, and thresholds to ipsilateral ear stimulation were significantly higher than thresholds to contralateral ear stimulation. In support of this finding, a significant increase in dendritic length and a change in their orientation in the auditory cortex contralateral to the ablated ear was observed in rabbits with neonatal unilateral ablation (192). Earlier studies in the cat of the anatomic consequences of cochlear ablation were restricted to adult animals. In these studies, lesions resulted in the shrinkage of cells in the deafferented cochlear nuclei (259) and contralateral medial nucleus of the trapezoid body (121). Neonatal cochlear ablation in gerbil (145, 234), however, has been reported to produce far greater anatomic changes in the central auditory pathways. The cochlear nuclei on the nonoperated side contained a greater number of cells projecting to the ipsilateral inferior colliculus and a reduced number of cells projecting to the contralateral inferior colliculus compared with controls (218, 234).

The increased input to the colliculus ipsilateral to the intact ear in gerbils after unilateral cochlear ablation in the early postnatal period was accompanied by signs of increased excitatory influence from the ipsilateral ear. Multiple unit activity (234) as well as single unit activity (145) dramatically increased in adult age in these animals, with more vigorous responses, broader dynamic ranges, and lower thresholds than in adult intact animals. The responses of inferior colliculus (IC) neurons to ipsilateral stimulation closely resembled those found in response to contralateral stimulation in the binaurally intact animal. Interestingly, the functional reorganization in pathways projecting to the IC was not accompanied by changes in synaptic density within the IC (83), since adult cats deafened neonatally in one ear did not exhibit changes in synaptic density with respect to normal hearing controls. The synaptic density in the IC was, however, significantly lower in cats deafened bilaterally (83). In later studies by Kitzes et al. (144), detailed structural changes were reported in the superior olivary complex of gerbils after unilateral neonatal ablation of the cochlea. Projections from the ventral cochlear nucleus to higher brainstem nuclei, which normally were directed to the contralateral side, instead were directed to individual nuclei of the superior olivary complex (medial and lateral superior olive, medial nucleus of the trapezoid body) on both sides after cochlea ablation. Such induced projections first appeared within 24 h of cochlear ablation and continued to develop over at least 11 subsequent days. Thus, before the day when the cochlea in the gerbil becomes functional (postnatal *day 12* or *13*), the ventral cochlear nucleus (VCN) has established specific ectopic projections to loci normally innervated by the VCN on the ablated side. All induced ectopic projections observed in neonatal animals

were also present in neonatally ablated adult animals. The fact that elements of the induced projections appear within 24 h of the cochlear ablation raises questions about the mechanism of induction. It was suggested (143) that neurons from the medial nucleus of the trapezoid body (MNTB) ipsilateral to the lesioned ear might release a chemotropic molecule after the growth cones of the ipsilateral calyciferous axons have already traversed the nucleus and are beyond the effective range of the molecule. With the loss of the normal source of calyciferous axons from the VCN on the operated side, the chemotropic molecule would then be available to influence proximal axons from the ipsilateral side. Neonatal destruction of auditory receptors is accompanied in experimental animals by a loss of spiral ganglion cells (SGC), by a loss of nerve cells in the cochlear nuclei, and by a reduction in the size of some nerve cells in the cochlear nuclei. Because these changes are partially reversible by electrical stimulation of the inner ear, comprehensive discussion of this topic is presented in section VI.

2. Ablations in adult animals

Although little is known at the present time about the processes subserving the formation of new connections after neonatal cochlear ablation, substantial data about changes in the brain stem auditory nuclei are available with respect to the effects of cochlear ablation in adult animals. Manipulations of the cochlea in adult gerbils (248) have been shown to produce transneuronal changes in the cochlear nucleus. The cross-sectional area of large spherical cells in the VCN was reduced by ~25% within 48 h of removing input to the VCN by ablation of the cochlea or by administration of tetrodotoxin to the cochlea. The authors concluded that the electrical activity of the auditory nerve fibers or sequelae of the electrical activity is a major factor in transneuronal regulation of cell size. Functional deafferentation in another study (27) was performed in adult guinea pigs by intracochlear infusion of the glutamate agonist α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), which is known to transiently disconnect inner hair cells from primary auditory dendrites (263, 264).

Measurements of immunostaining intensities demonstrated rapid and reversible changes in calcium-binding protein levels. Twenty-four hours after AMPA treatment, calretinin immunostaining was reduced in deafferented neurons of the cochlear nuclei and their axons of the superior olivary complex. In contrast, calbindin D28k immunoreactivity levels by this time were higher in deafferented neurons of the medial nucleus of the trapezoid body and their axons in the lateral superior olive. Parvalbumin immunostaining was also generally increased in deafferented neurons, but the changes were less evident and more complex. Normal levels of all three calcium binding proteins were reached within 5 days after AMPA treatment, when afferent activity had almost completely recovered. Apparently the increased buffering capacity in deafferented neurons, as indicated by rises in calbindin D28k and parvalbumin immunostaining, may be involved in the mechanisms promoting neuronal survival after loss of sensory input. Increases in calbindin D28k expression in brain stem auditory nuclei were also observed in mature rats after permanent unilateral cochlear ablation (67).

Calbindin is characteristically expressed in many auditory brain stem nuclei during ontogeny and disappears from many of these nuclei during maturation. Growth-associated protein (GAP)-43 shows a similar time-limited expression during ontogeny (106). Extensive data link the presence of GAP-43 to axonal elongation and synapse formation during development. While it is expressed at high concentrations in cochlear nuclei and the superior olivary complex on the first postnatal day in the rat, by the 16th postnatal day the immunoreactivity is almost lost, with only discrete levels persisting to adulthood. However, GAP-43 was expressed de novo in fibers and boutons of the ipsilateral cochlear nucleus after unilateral cochlear ablation in adult rats (110). The occurrence of GAP-43 after cochlear ablation in adult animals suggests that sudden loss of spiral ganglion cells leads to a reactive synaptogenesis in several auditory brain stem nuclei. Recent biochemical studies (320, 321) also suggest that after unilateral cochlear ablation in young adult guinea pigs, changes develop in glycinergic and GABAergic inhibitory transmission in the brain stem nuclei. Glycinergic transmission is persistently weakened ipsilaterally in the ventral cochlear nucleus and lateral superior olivary nucleus (LSO) and bilaterally in the dorsal cochlear nucleus (DCN).

Initial experimental results, in which changes in the function of the central auditory system after cochlear ablation in adult animals were studied, did not show any significant effect on the neuronal responses in the IC. Unilateral cochlear ablation in adult gerbils did not affect the proportion of IC neurons excited by the ipsilateral ear (234). Large lesions of the cochlear nucleus in the adult gerbil had no apparent effect on the responsiveness of single neurons in the contralateral IC to stimulation of the intact ear (219). However, experiments in the ferret (220) found that even after unilateral cochlear ablation in adult animal, the proportion of neurons excited from the intact ear in the ipsilateral IC was unusually high. In subsequent experiments (216), performed in the ferret auditory cortex, the authors confirmed that the adult ferret auditory system responded rapidly and dramatically to cochlear ablation. The topographic representation of the ipsilateral ear in the primary auditory cortex expanded after ablation of the contralateral cochlea. Also, the proportion of units in the AI driven by stimulation of the intact ear substantially increased. While in control animals the ipsilateral

ear provided excitatory drive to only ~50% of the recording sites that were excited by contralateral stimulation, after acute cochlear ablation a much more widespread distribution of ipsilateral excitation was found. "Acute" cochlear ablation in the ferret (i.e., within 24 h before recording) produced a quantitative reduction in mean unit thresholds and an increase in the spontaneous discharge rate of cortical neurons on the side of the intact ear relative to normal, binaurally intact animals. Although these experiments have shown that changes in the excitability of the central auditory system after cochlear ablation occur very early, it has been demonstrated (216) that the number of loci in the ferret IC excited from the ipsilateral ear increased with the time of survival after cochlear ablation. Similarly, the thresholds of neuronal responses to ipsilateral stimulation decreased with survival time after ablation. These results contradict a simple unmasking hypothesis (35) of the changes in excitability, which would predict that all changes occur suddenly. The term *unmasking* implies immediate release from suppression after ablation of an inhibitory input. This unmasking may be contrasted with longer term changes that include the modification of existing synapses, synaptogenesis, and the formation of new connections (43, 44).

Results similar to those in the ferret were obtained in experiments in adult guinea pigs with quasi-complete hair cell destruction induced by injection of an ototoxic antibiotic into one ear (254). The thresholds of evoked potentials in the auditory cortex ipsilateral to the nondamaged ear decreased, and the amplitudes increased over the course of several days or weeks after hair cell destruction. These results also do not support the unmasking hypothesis, the slow progress of change during several days or weeks after cochlear lesion speaks in favor of less dramatic and more structural changes.

B. Effects of Partial Cochlear Lesions

1. Lesions induced at birth

Initial experiments with partial lesions of the cochlea in newborn animals were performed in cats where changes were found in the primary auditory cortex (87). A neonatal high-frequency loss was induced by injections of the ototoxic antibiotic amikacin in newborn kittens, and tonotopic maps were constructed in adult animals after 12-mo survival. As in experiments by Robertson and Irvine (280) with adult guinea pigs, the AI in the cat was extensively reorganized with regions that in normal nonlesioned controls were excited by high frequencies being taken over by lower frequencies, primarily those associated with the border of the cochlear lesion (see below for details). However, retrograde tracer injections into different regions of the AI produced a normal pattern of labeling in the ventral division of the medial geniculate body (MGB) (318). The deafened cats did not develop more divergent thalamocortical projections compared with normal control animals, indicating that an abnormal spread of thalamocortical afferents across the frequency domain of the AI is not responsible for the altered cochleotopic map in these neonatally deafened animals.

The effects of cochlear lesions produced by injections of amikacin in newborn animals were studied further in the inferior colliculus in chinchillas (86), i.e., in a precocious animal. As a result of the cochlear lesion, the tonotopic maps in the IC of adult chinchillas were substantially reorganized, usually with a large "monotonic" or "isofrequency" region in the ventral part of the central nucleus of the IC, i.e., in the area where normally high frequencies are represented. The tuning curves of neurons in this expanded region were pathological and their tuning, which was almost identical, corresponded with the tuning of the boundary areas of the cochlear lesion.

2. Lesions induced in adult animals

In contrast to the plasticity exhibited by the developing nervous system, it was for many years generally assumed that representational maps in adult animals were stable and not susceptible to change. Studies over the last 20 years have shown that this is not the case and that sensory projection areas of the adult brain are subject to reorganization after peripheral receptor lesions. In the auditory system, a pioneering study was published in 1989 by Robertson and Irvine (280), who induced restricted mechanical lesions of one cochlea in mature guinea pigs and assessed the extent of the resultant hearing loss by recording the compound action potential audiogram and by histological examination of the cochlea. The lesion produced a relatively sharp notch of decreased peripheral sensitivity over a range from ~10 to 20 kHz, associated with a discrete region of abnormal inner and outer hair cells at the corresponding cochlear location (Fig. 1). The frequency organization of the auditory cortex in the hemisphere contralateral to the lesioned cochlea was investigated with a microelectrode mapping technique 35–81 days after cochlear lesioning. The region of cortex that in normal animal would be occupied by an orderly and continuous representation of frequencies from 10 to 20 kHz was found to be almost entirely occupied by enlarged representations of limited frequency ranges corresponding to the borders of the cochlear lesions (9.9–10.8 kHz and 20.6–22.0 kHz). The responses of neuronal clusters in the reorganized regions of the cortex were strong, and their thresholds at the newly acquired characteristic frequencies were comparable to those observed in normal control animals.

The changes in the representation of the lesioned cochlea in the contralateral hemisphere were assessed using acoustical stimulation of the lesioned ear. However,

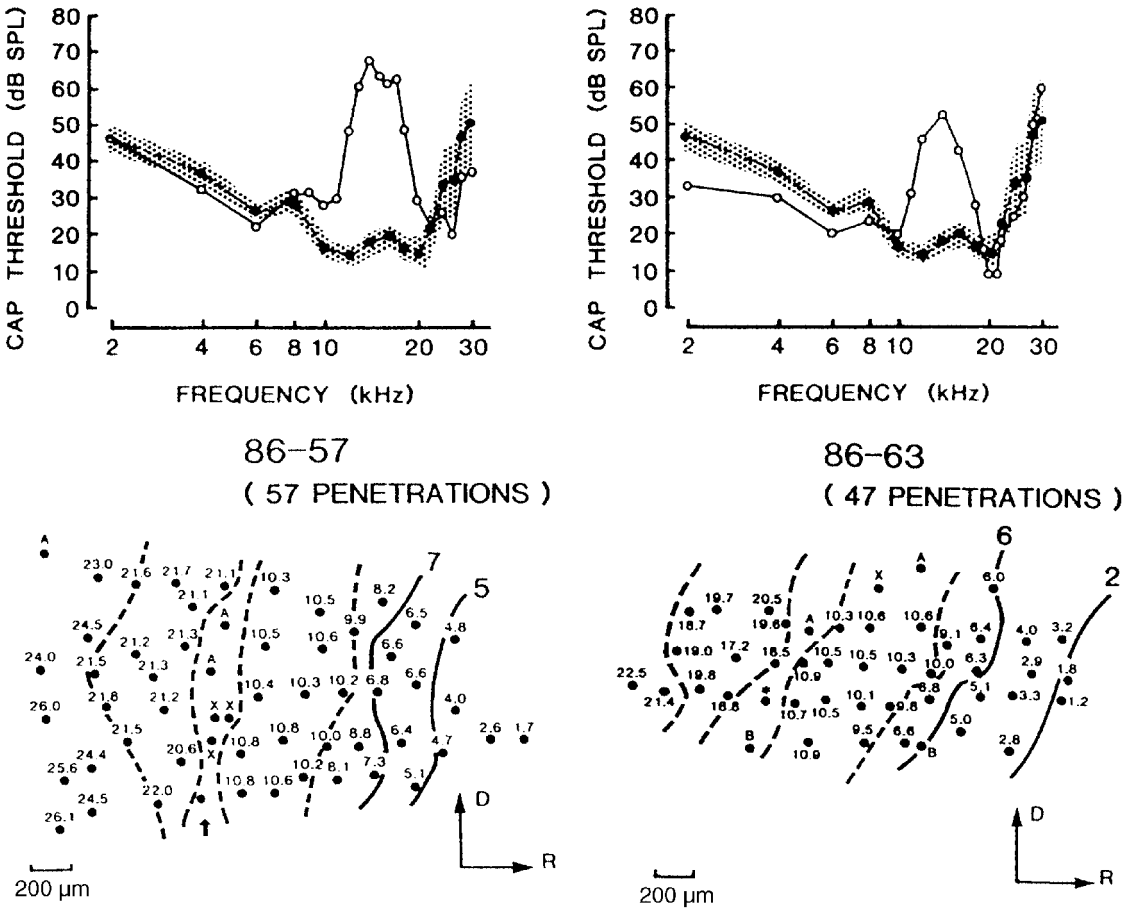

FIG. 1. Two examples of "notch"-type lesions in the cochlea with corresponding cortical frequency maps. *Top panels*: compound action potential (CAP) audiograms. The postrecovery audiogram for each animal (open circles, solid lines) is compared with the mean audiogram for 10 normal animals (solid circles, broken line). Shaded areas around the normal mean audiogram show 1 SD. *Bottom panels*: frequency organization of the auditory cortex after lesion. Each dot represents the location on the cortical surface of an electrode penetration. The number beside each dot is the characteristic frequency (CF) in kHz of clusters at that point. Points marked X were unresponsive to acoustic stimulation. Points marked A were acoustically responsive, but a clear CF could not be assigned. Lines are approximate isofrequency contours drawn by eye through loci of the same CF as indicated by the numeral at the end of each line. Broken lines delineate areas of expanded frequency representations with sensitive drive. D, dorsal; R, rostral. [From Robertson and Irvine (280). Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.]

as discussed above, the unilateral ablation of the cochlea produces changes in the representation of the unlesioned ear in the inferior colliculus and auditory cortex. Therefore, Rajan et al. (268) investigated the effects of unilateral restricted cochlear lesions in adult cats on the representation of the lesioned and normal cochleas in the primary auditory cortex (area AI) contralateral to the lesioned ear. High-frequency loss, with edge frequencies in the range of 18–24 kHz, was produced by mechanical lesions of the cochlea. In confirmation of the study in adult guinea pigs (280), in adult cats 2–11 mo after a unilateral cochlear lesion, the map of the lesioned cochlea in the contralateral AI was also altered so that the AI region in which the frequencies with lesion-induced elevations in cochlear neural sensitivity would have been represented was occupied by an enlarged representation of lesion-edge frequencies. There was no topographic order within this enlarged representation. In contrast to the change in the map of the lesioned contralateral cochlea, the map of the unlesioned ipsilateral cochlea did not differ from those in normal animals. This finding is in sharp contrast to the results of experiments with complete unilateral ablation of the cochlea in which the excitatory influence of the unlesioned ear on the central auditory system was strengthened. A comparison of the tuning curves of cortical neurons in the reorganized area with those in normal control animals did not disclose any essential differences. The tuning curves were slightly, but not significantly, less sharply tuned, and in some animals the latencies of responses were significantly shorter than normal. Further evidence bearing on the effects of experimentally produced cochlear lesions in adults on the fre-

quency organization of the auditory cortex was obtained in adult macaques who were treated by kanamycin and furosemide to produce a high-frequency hearing loss (303). When the cortex was mapped 80–90 days after ototoxic treatment, the high-frequency region of the AI was found to be occupied by an enlarged representation of lesion-edge frequencies.

The lack of alignment of ipsilateral and contralateral projections in the AI of the adult cat after unilateral restricted lesions led to the conclusion that the plastic changes in the contralateral AI are a product of changes at the subcortical level. When partial cochlear lesions were performed in the same manner as in previous experiments looking at changes in the auditory cortex (268), no plasticity of the frequency maps was found in the dorsal cochlear nucleus (267) and only patchy signs of plastic changes were observed in the central nucleus of the inferior colliculus. Similarly, no evidence of reorganization was reported in the dorsal cochlear nucleus of adult hamsters in which restricted cochlear lesions were produced by intense noise exposure (132). These data suggest that the pathway from the dorsal cochlear nucleus to the central nucleus of the inferior colliculus is not involved in the lesion-induced reorganization in the colliculus.

One possible explanation of the mechanisms of cortical map reorganization is based on the loss of cortical inhibition, specifically surround inhibition. Receptor organ damage leads to an anatomically defined loss of inhibitory inputs in the somatosensory and visual cortices (e.g., Refs. 72, 99, 360, 372) and a physiologicaly defined unmasking of normally silent inputs in the deprived sensory cortex (29). Surround inhibition is inhibition deriving from the receptor surface regions adjacent to those providing excitation, and it has been shown to restrict physiological response spread within cortical neurons. However, in the auditory system, receptor organ damage produces a loss of surround inhibition in the auditory cortex without topographic map plasticity (266). The level of inhibition was examined in cats with restricted unilateral cochlear damage. The threshold shifts assessed by measurement of the compound action potential were ~25 dB or less. For assessing the inhibitory parts of the neuronal tuning curve, a conditioning (forward masking) experimental design was used involving the presentation of two successive stimuli. The second of these tones was fixed at the cortical neuron's characteristic frequency (CF; the frequency to which the neuron is most sensitive) and the first was varied in frequency and intensity outside the excitatory response area of the cortical neuron. This procedure revealed that surround inhibition was almost absent in cortical neurons with CFs within the cochlear hearing loss range (Fig. 2). This was in sharp contrast to neurons with a CF outside the area of hearing loss and with neurons from normal control animals. In the cortical area corresponding to the lesioned cochlear region, further signs of decreased inhibition were also present: nonmonotonic spike-intensity functions were less numerous, the responses to white noise stimulation exhibited less inhibitory influences, and some neurons expressed dual response lobes in the excitatory response areas. However, the loss of surround inhibition was not accompanied by a reorganization of the topographic CF map. It is therefore probable that the loss of surround inhibition is not responsible for the topographic reorganization of the auditory cortex after restricted peripheral lesions. The results, however, demonstrate clearly that hearing loss, and in this case hearing loss induced by noise in most animals, results in a profound decrease of inhibition in the auditory cortex and possibly also in some subcortical structures. This is in agreement with data obtained in

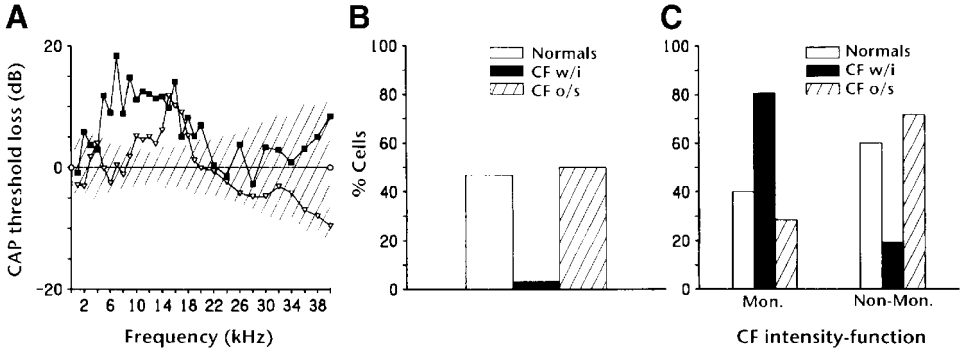

FIG. 2. Restricted cochlear hearing losses result in the near absence of cortical surround inhibition, which alters neuronal response patterns shaped by inhibition. *A*: examples of cochlear hearing losses in two cats. Cochlear hearing sensitivity, measured as frequency-specific thresholds for the auditory nerve CAP, is expressed as threshold loss relative to mean normative thresholds, which are plotted as zero. The hatched area represents the range within 1.64 SD of the mean normative threshold. *B*: incidence of surround inhibition in primary auditory cortex (AI) neurons of normal animals (open bars) and in neurons of test animals grouped according to whether the neuron's CF was at a frequency within the range with CAP threshold losses (test neurons, solid bars) or at a frequency outside this range (control neurons, hatched bars). *C*: patterns of responses to pure tone stimuli at CF: incidence of AI neurons with monotonic or nonmonotonic intensity functions. AI neurons were grouped as detailed for *B*. [From Rajan (266)].

experiments where the effects of noise exposure on the auditory cortex function were assessed (see sect. IV).

III. CHANGES RESULTING FROM AGING

A common denominator for the cause of plastic changes in both total ablations or partial lesions of the cochlea is the loss of receptors, the hair cells. Apparently it is not relevant whether the loss is induced by mechanical intervention or by the destruction of hair cells with ototoxic drugs. In addition, several other causes of hair cell loss exist, which may be accompanied by plastic changes in the central auditory system. Damage of hair cells may result from overexposure of the auditory system to noise or as a consequence of aging. The latter case is usually characterized as presbycusis. Presbycusis in humans refers to a constellation of age-related auditory deficits that include a loss of hearing sensitivity and a decreased ability to understand speech, particularly in the presence of background noise. The hearing loss tends to accelerate with age, with high-frequency losses exceeding low-frequency losses at all ages. Data from large populations screened for noise exposure and otologic disease (for review see Ref. 379) show a progressive increase of hearing loss amounting to ~20 dB at frequencies below 1 kHz, when hearing thresholds at ages 30 and 70 years are compared, and increasing to 60 dB difference at 8 kHz (337). Age-related hearing deficits in humans have usually been attributed to changes in the cochlea, including a loss of sensory cells, atrophy of stria vascularis, and a loss of spiral ganglion cells. However, an important part of presbycusis consists of changes in the central auditory system. The changes were demonstrated in many recent animal experiments, particularly in mammalian species with a relatively short life span, such as mouse, rat, or gerbil. The results of these experiments will be briefly reviewed further.

A. Animal Models of Presbycusis

1. *Animal strains used in the study of presbycusis*

Animals suffer a similar deterioration in hearing function with aging as do humans. However, the extent of the deterioration is different not only among animal species but also within a species. Particularly in mice, there are many inbred strains that exhibit rapid progress in presbycusis as well as many mutants that succumb to progressive hearing loss with aging.

One of the best-characterized models of human presbycusis is the Mongolian gerbil (2, 20, 21, 81, 97, 206, 208, 300, 301, 341). The gerbil has an audibility curve similar to that of humans, with greatest sensitivity around 4 kHz. It is an outbred strain, and it is therefore genetically diverse, like humans. As a result, variability in the magnitude of hearing loss that gerbils develop over their life span is extremely high. Another model of human presbycusis is represented by the C57BL/6J (C57) strain of mouse (101, 109, 188, 189, 200, 358, 377, 379–383, 385, 386, 388–390). In contrast to gerbils, all individuals of the C57 strain are genetically identical. The disadvantage of this model of human presbycusis is that the audibility curve in the C57 mouse is shifted upward by several octaves, with greatest sensitivity around 16 kHz (102, 166, 188, 200). The C57 mouse strain, which demonstrates a progressive auditory decline with onset at an early age, is usually compared with another model, the CBA/J (CBA) mouse strain, which displays a moderate auditory impairment with onset late in life (100, 102, 109, 136, 165–167, 245, 307, 310, 317, 373, 379, 384, 387–390). Another model, used particularly in studies of the biochemical aspects of presbycusis, is represented by the Fischer 344 rat or Fischer 344 × Norway F1 strain of rats (32, 64, 201–203, 241, 242, 309, 396). Compared with human, the audibility curve in rat is (as in the mouse) shifted upward to higher frequencies with the best sensitivity around 16 kHz (334).

The three mentioned animal models now dominate presbycusis research; limited data are also available on hearing loss connected with aging in other species. Changes in the cochlea and in the central auditory system with aging were previously described in guinea pig (39, 50, 51, 112), chinchilla (23, 187), cat (85), and monkey (45, 93). The main obstacle for detailed analysis of presbycusis in these species relates to their long life spans, which in rhesus monkey exceeds 30 years. All animal models are of limited value in explaining the sequelae of presbycusis in humans, since in humans the main problem of presbycusis is the deterioration in speech comprehension (see sect. III*B*).

2. *Morphological, physiological, and behavioral changes accompanying aging in animals*

A characteristic feature that dominates cochlear pathology in presbycusis in animal models is a loss of hair cells in the inner ear. For example, in the C57 mouse strain, the genetically programmed pattern of sensorineural loss starts in early adulthood, ~2 mo of age, and progresses to near total deafness by the second year of life (166, 378). The cochlea undergoes progressive hair cell loss, starting in the basal coils (high-frequency region) and progressing to involve increasingly lower frequencies along the cochlear membrane (102, 317). A loss of both outer hair cells (OHC) and inner hair cells (IHC) is present, although the percentage of lost OHC is always higher. In contrast, the CBA mouse shows little evidence of hair cell damage until late in life, i.e., until 18 mo of age. By 26 mo of age, the OHC losses in the apex (low-frequency region) and base of the cochlea in the CBA mouse

equal approximately one-half of the total number. At the same stage, one-quarter of IHC are lost. The hair cell loss is, in the C57 mouse, accompanied by a loss of spiral ganglion cells with nearly complete loss in the basal cochlea during the second year of life (379). The measurements of hearing threshold shifts with evoked potentials during the life span of C57 mice reflect hair cell loss in the inner ear (378). Threshold shifts are mostly expressed at high frequencies, later progressively spreading to low frequencies.

From species with life spans longer than mice or rats, more extensive data about the anatomic and functional consequences of aging are available in guinea pigs and chinchillas.

In guinea pigs, cochlear pathology has been studied in animals up to an age of 5 years. No significant loss of hair cells was seen in the basal or middle turn of the cochlea of aged animals (111). In the apical (low-frequency) turn, there was a significant loss of hair cells in all rows of the outer hair cells (up to ~20%), most severe in the third row. There was no loss of apical inner hair cells in the aged animals. The apical loss of hair cells corresponded with the originally described decrease in the numbers of spiral ganglion neurons, which also occurred near the apex (39). Recordings of auditory brain stem responses (ABR) (51, 112) demonstrated a marked elevation of hearing thresholds in this species; however, the reason for this was considered to be conductive hearing loss (112). There were no significant age-related changes in the interpeak intervals of the ABR. Detailed histopathology in chinchillas, at ages up to 19 yr, demonstrated small but progressive losses of OHC and IHC (with the outer row of OHC most severely affected), more expressed at the apex and base. In many cases IHC losses were accompanied by damage to spiral ganglion cells (23). A later study by McFadden et al. (187) confirmed the losses of OHC and IHC in the basal and apical regions of the cochlea in aged chinchillas. The losses were paralleled by decreases in distortion product otoacoustic emissions and small but significant declines in auditory sensitivity, indicated by measurements of evoked potentials with high-frequency losses exceeding low-frequency losses.

Although most changes in hearing function connected with aging may be considered as a reflection of cochlear pathology, the results of several studies suggest that changes in the function of the central auditory system might appear as well. Willott (377, 378) compared the activities of neurons in the inferior colliculus of C57 and CBA mice. The results showed several changes in the function of neurons in the fast-aging C57 mouse, which were not present in the CBA mouse. As high-frequency sensitivity in C57 mice declined as a result of cochlear pathology, neurons in the ventral IC that normally have low thresholds for high-frequency tones could no longer respond to them. The best frequencies (the frequency for which a neuron has the lowest threshold) of ventral IC neurons shifted from high to middle frequencies so that the best frequencies tended to be similar throughout the IC. That is, tonotopic organization was severely disrupted in middle-aged C57 mice. The "shifted" best frequencies had thresholds that were lower than the thresholds of the same frequencies in the tuning curve "tails" of neurons in the same location in young mice. As hearing loss progressed even more, thresholds for all frequencies were eventually elevated. Willott and colleagues (382, 390) later completed the study by investigating single and multiple unit responses in the cochlear nuclei and auditory cortex of the C57 mouse. In principle, changes in the auditory cortex were similar to those observed in the IC, i.e., with aging virtually the entire auditory cortex contained neurons with best frequencies in the middle-frequency range. In contrast, neurons in the ventral nucleus of the C57 mouse did not show the age-related sensitization of tuning curve tails seen in the IC and auditory cortex (AC) neurons from high-frequency tonotopic regions. Altogether the results demonstrated that the plastic changes in the thresholds of tuning curves, observed in the aging C57 mice, are limited to regions of the central auditory system higher than the ventral cochlear nuclei.

Many studies of plasticity mechanisms have suggested that a diminished inhibition could be involved in changes observed during brain aging. In the central auditory system such investigations were mostly performed in the IC of the Fischer 344 rat. The IC has been shown to display age-related changes including decreased numbers of GABA immunoreactive neurons, decreased basal levels (concentrations) of GABA, decreased GABA release, decreased glutamate decarboxylase levels, decreased $GABA_B$ receptor binding, decreased numbers of presynaptic terminals, and subtle $GABA_A$ receptor binding changes (33, 34, 201). Age-related changes of the $GABA_A$ receptor in the IC of young-adult, middle-aged, and aged Fischer 344 and Fischer 344/Brown-Norway F1 hybrid rats were related to receptor subunit composition and receptor function (32). In both strains, the aged group exhibited significant increases in γ_1-subunit protein and a decrease in α_1-subunit protein. These results suggested an age-related change in $GABA_A$ receptor composition. Age-related changes have also been noted in calbindin D-28k and calretinin immunoreactivity in the IC of young and old C57 and CBA mice (403). As mentioned above, the CBA/CaJ mouse maintains good hearing until very late in life, whereas the C57Bl/6 strain exhibits severe sensorineural hearing loss at an early age. Cell counts revealed a 22.3% decrease in the number of CB+ cells in old CBA mice and a 25.1% decrease in old C57 mice. Calretinin immunoreactivity was high in the pericentral regions of the IC, but the central nucleus was devoid of CR+ cells. The pericentral parts of the IC showed increases in the number of CR+ cells, but

only in the old CBA mice. No significant change was observed in the old C57 mice. The increase in CR+ cells was interpreted as a possible compensatory adaptation to the decrease in CB+ cells. Changes with aging were observed also in the structure of the IC in the C57 mice (135). A significant loss of the axosomatic synapses on the principal neurons in the central nucleus of the IC started at 6 mo of age (early middle age) and became progressively severe into old age (24 mo). In contrast, in the CBA mouse, aging was not accompanied by changes in the number or type of synapses, the length of synaptic apposition, or the size of the synaptic terminal area. The preservation of synapses on principal neurons in this strain suggests that synaptic loss is not an inevitable event in aging but may be related to the preservation of peripheral auditory function and input to the neurons (136).

The changes accompanying aging were demonstrated in the IC of Fischer 344 rats also with electrophysiological methods (241). A comparison of responses of single units to acoustical stimuli in aged and young rats revealed that although the average threshold increased from 25.4 dB sound pressure level (SPL) in young rats to 56.1 dB SPL in aged rats, no differences were noted in spontaneous activity, first spike latency, dynamic range, percentage of units with nonmonotonic contralateral CF tone rate-intensity functions (RIFs), or percentage of units sensitive to change in CF tone presentation rate. In aged rats, a higher percentage of units were poorly responsive to auditory stimulation than in young animals; there was a reduction in the maximum discharge rate, an increase in the percentage of units classified as onset in their temporal response pattern, and an increase in the breadth of the isointensity functions at 30 dB above threshold. Age-related changes in the central nucleus of the IC (CIC) frequently differed from those observed in the external cortex of the IC (ECIC). For example, the percentage of units classified as having nonmonotonic contralateral tone RIFs decreased with age in the CIC but increased with age in the ECIC. Altogether these results support the hypothesis that there is an age-related shift to higher intensities in the working range of most CIC units along with a small, selective deficit in inhibitory processing. However, despite peripheral deficits that lead to reduced input to the IC and neurochemical changes affecting neurotransmitter levels, IC neurons in aged rats were able to respond to simple auditory stimuli in a fashion quite similar to that observed in young rats. Even though a decrease in GABA and GABA receptor levels in the old Fischer 344 rat IC was present, the binaural interaction as measured by responses of single units in the IC to binaural stimuli essentially did not differ between young and old Fischer 344 rats (242). Similar results were observed in the superior olivary complex (64), which together with results from the IC demonstrate that the mechanisms of binaural interaction might not be significantly influenced by aging.

Changes in the levels of mediators and their receptors accompanying aging were demonstrated in the Fischer 344 rat not only in the IC but also in other parts of the central auditory system. In the cochlear nucleus, a significant age-related decrease in [^{3}H]strychnine binding was observed, suggesting a decrease in strychnine-sensitive glycine receptors (203). Similarly in the neocortex of Brown Norway $\times$ Fischer 344 F_1 rats, an age-related depletion of presynaptic boutons as indicated by a decrease in synaptophysin immunostained punctae (396) was found.

Interesting aspects of the auditory system's plasticity were shown by the results of studies in which animals were exposed to an augmented acoustical environment, i.e., their auditory system was continuously stimulated by broad-band noise for several months (348, 391, 392). Such procedures were able to ameliorate aging-elicited changes in the auditory function in strains of mice with progressive hearing loss. Mice of strains that exhibit high-frequency hearing loss during young adulthood [the C57BL/6J strain (C57)] or around the time of weaning/adolescence [the DBA/2J strain (DBA)] were exposed, starting at age 25 days, to a 70 dB SPL broad-band noise for 12 h every night. The augmented acoustical environment was maintained until age 14 mo in C57 mice and 9 mo in DBA mice. Control mice were age matched and maintained under normal vivarium acoustic conditions. The ABR, acoustic startle response amplitude, and prepulse inhibition (PPI) were used to assess the function of the auditory system. Exposure to the augmented acoustical environment resulted in improved auditory performance in both strains (better PPI, lower ABR thresholds, larger startle amplitudes). Similar results were obtained in mouse strains that exhibit various degrees and time courses of progressive hearing loss (BXD-22, BXD-12, BXD-16, BXD-14, BALB/cJ) and in normal-hearing CBA/CaJ mice. The augmented acoustical environment was maintained for at least 30 days in each strain. Exposure to the augmented environment resulted in improved auditory performance (better PPI, lower ABR thresholds) when hearing impairment was present, but not when hearing was normal. The ameliorative effects occurred irrespective of the mouse's age at the onset of hearing loss, as long as the initiation of treatment with the augmented environment preceded the occurrence of severe hearing loss. If the treatment was delayed beyond such a point, loss of threshold sensitivity progressed as usual, although PPI could still benefit. The results have shown that augmented environment treatment can slow, but not prevent, the occurrence of severe genetically determined hearing loss. The effects of the exposure to an augmented acoustical environment may be compared to some extent with the effects of similar

experiments in which animals were exposed to a so-called enriched environment (for review see Ref. 260).

B. Presbycusis in Humans

The signs of presbycusis in humans are similar to those observed in experimental animals (316, 379). Loss of IHC is typically present in the basal turn of the cochlea, whereas the loss of OHC is more scattered, spreading up to the apical part. The loss of OHC is always more pronounced than the loss of IHC. Less severe signs of degeneration in the cochlea comprise the occurrence of different disarrays of stereocilia of hair cells, including the occurrence of giant stereocilia. Concomitantly with the loss of hair cells, presbycusis is accompanied by a loss of spiral ganglion cells, which usually comprises the loss of peripheral dendrites as well as central projections, i.e., auditory nerve fibers. The efferent system seems to be more robust and does not degenerate to the same extent as the afferent system. In the central auditory system a marked reduction in the cell size of neurons in the ventral cochlear nucleus was found in subjects with profound hearing loss (221). The size of neurons was larger in subjects with greater survival of cochlear ganglion cells.

The results of electrophysiological investigations of the aging auditory system correspond with the described morphological changes. The amplitude of the acoustic reflexes decreases with age similarly to the amplitude of auditory brain stem potentials. The latencies of ABR waves may be slightly prolonged. In some cases increases in the amplitude of middle latency responses (MLR) at higher intensities of sound stimulation were found, probably as a sign of a decreased amount of inhibition in the central auditory system (397). Changes with age in the hearing thresholds for pure tones have been well documented in many audiometric studies (e.g., Ref. 337) (Fig. 3). In listeners screened for the absence of subjective indications of hearing loss of different origin than aging, the thresholds for low-frequency tones change little with age, while in sharp contrast, high-frequency sensitivity is greatly diminished (for review see Ref. 379). The decline in the hearing sensitivity is different for men and women; in men it declines twice as fast as in women at most ages and frequencies (249, 337). Longitudinal declines in hearing sensitivity are detectable among men by age 30, but the age of the onset of the decline is later in women at most frequencies. Women have more sensitive hearing than men at frequencies >1,000 Hz, but men have more

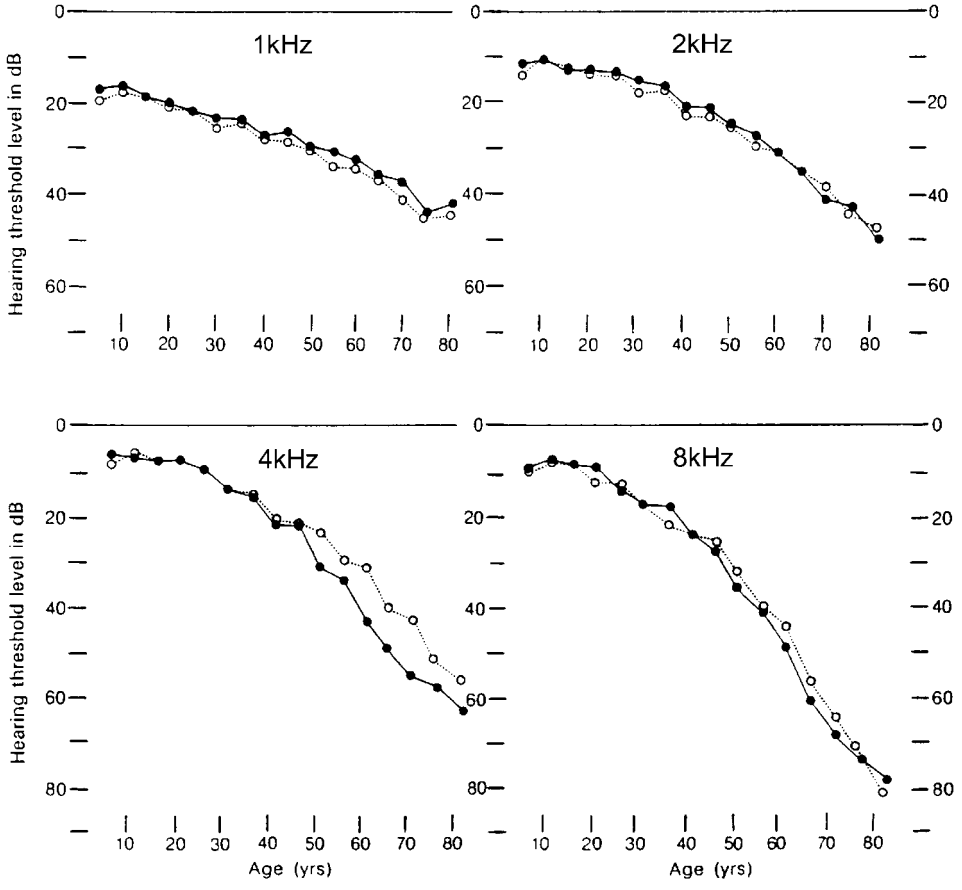

FIG. 3. Effect of age on hearing threshold levels in decibels at 1, 2, 4, and 8 kHz. Solid circles represent male, and open circles represent female. [From Takeda et al. (337), copyright 1992 Springer-Verlag.]

sensitive hearing than women at lower frequencies (246, 249).

In addition to increases in hearing thresholds, elderly listeners manifest deficiencies in their ability to process information about frequency, intensity, time, and space. In most cases the presbycusis is based on cochlear impairment, a typical sign of which is the occurrence of a phenomenon called loudness recruitment. In this case relatively small increments in sound intensity are perceived as disproportionate increases in loudness. Loudness recruitment is present in 20–50% of older listeners (379). Frequency resolution declines with aging as hearing loss increases (177). When hearing level is accounted for, there is only a minor decline in age-dependent frequency resolution. Temporal resolution, which is usually measured as gap detection thresholds, declines with sensorineural hearing loss. However, in older adults with good hearing, significantly higher thresholds in gap detection studies were also found. Older adults who were matched to a group of younger listeners with respect to their audiometric thresholds had gap detection thresholds that were ~30% higher than those of the young listeners (302, 311, 319). Spatial hearing based on binaural cues also deteriorates with aging. Higher thresholds for interaural time differences were found in elderly adults with clinically normal hearing than in matched young listeners (319), and similarly, the results of a test of binaural hearing based on the precedence effect were found to be affected by age (40). Because in both studies only subjects without peripheral hearing loss were included, the results speak in favor of specific changes in the central auditory system with aging.

By far the most important function of the auditory system in humans is speech recognition. Speech understanding deteriorates with aging, especially in situations in which the voice of the speaker is accompanied by a noisy background or by other voices. The details of this topic are, however, out of the scope of the present review. Improving speech recognition is an important goal in the treatment of hearing loss with hearing aids. There is only limited information available about improvements in hearing function with long-term wearing of hearing aids (240). For example, it has been shown that in bilateral, hearing-impaired subjects using a single hearing aid, speech identification for the unaided ear declined over a long period of time relative to the performance of the normally aided ear after unilateral amplification (308). In other experiments (73) with long-term users of a single hearing aid, the normally aided ear performed better for speech identification in the presence of background noise than the unaided ear at high SPL (>75 dB). At low SPL (<75 dB), the situation was reversed, i.e., the unaided ear showed better performance than the normally aided ear. The advantage of the normally aided ear only became apparent after listeners had used their hearing aid for 4–6 wk (74). The advantage at high presentation levels is probably the result of increased sensitivity to intensity changes at levels to which the ear is normally exposed. As the tested listeners had sloping sensorineural hearing impairment that was bilateral and symmetric, their hearing aid provided gain at the impaired, higher frequencies, and little to no gain at frequencies that were close to normal hearing levels. This was confirmed in intensity discrimination tests in which a greater sensitivity to changes in intensity was observed in a normally aided ear tested without the aid than in the unaided ear at sound pressure levels greater than 85 dB (281). Plastic changes in normally aided ears definitely do occur; research in this topic is just beginning. For example, because hearing aids are almost always used only unilaterally, very little is known about benefits of bilateral hearing aids.

In summary, presbycusis is a process that is present in all mammals. However, in humans it comprises not only the loss of auditory receptors and the resulting changes in the central auditory system, but also inevitable impairment of speech comprehension. The practical solution of the problems associated with presbycusis in humans, such as auditory threshold shifts, intensity recruitment, and loss of frequency and temporal resolution, lies in refinements of prosthetic devices such as hearing aids. A knowledge of the plastic changes in the central auditory system occurring in presbycusis may open new vistas in the pharmacological treatment of the impairment. For example, it will be necessary to understand the influence of decreased inhibition in the central auditory system on the manifestation of presbycusis symptoms with the aim of starting rational treatment. Practical outcomes may also be expected from further studies of the long-lasting effects of wearing hearing aids. An understanding of the plastic changes in the auditory system during aging should serve to ameliorate the negative sequelae of this inevitable process or at least move the problems to an older age.

IV. NOISE-INDUCED CHANGES IN THE AUDITORY SYSTEM

A. Changes in the Cochlea

Noise exposure produces various effects in the auditory system, the detailed description of which is out of the scope of this review. For more information several other reviews can be consulted (11, 42, 292, 328).

The usual characterization of noise-induced changes in the auditory system is based on changes in the hearing threshold. Short-term exposure to noise with relatively low sound intensities results in a temporary hearing loss with a limited threshold shift and recovery of hearing sensitivity after some time (temporary threshold shift;

TTS). Exposure to high intensities of noise even for a short period produces damage in the cochlea without recovery in hearing sensitivity; the threshold shifts are therefore permanent (permanent threshold shifts; PTS).

While the primary reason for PTS is the loss of OHC and IHC in the cochlea, the mechanisms of TTS still remain to be elucidated. The primary source of mechanical input to the cochlear hair cells during acoustic stimulation is the relative shear between the tectorial membrane and the hair cells' apical parts produced by basilar membrane motion. The displacement of stereocilia modulates their transducer conductances. Stimulation by a loud sound may cause changes in the mechanical properties and consequently in the conductances of hair cells. Indeed, several studies have indicated that intense acoustical stimulation changes the micromechanical properties of the sensory hair bundle at the apical pole of the hair cells (297, 298). Damage to the stereocilia correlates well with alterations in the tuning curves of auditory nerve fibers (169).

Calcium ions may play a potential role in the pathological processes following acoustical overstimulation, as significant elevations of Ca^{2+} were found in the cytoplasm of OHC after acoustic overstimulation (68). Similarly, the increased permeability of the endolymph-perilymph barrier to potassium and sodium ions after noise exposure (126, 147, 148, 290) could be involved in the mechanisms of TTS.

Another mechanism for the TTS has been proposed in connection with changes that occur in the synapses between IHC and peripheral dendrites of the primary auditory neurons, i.e., spiral ganglion cells. Acoustic trauma causes a disruption of dendrite endings below the IHCs, leading to synaptic uncoupling. The dendrite damage might be due to an excessive release of the neurotransmitter glutamate from the IHCs, which is toxic to the structure and function of the primary auditory neuron (262–264). Excess glutamate in the extracellular space below the IHCs could result in permeability changes in the postsynaptic membrane of the dendrite. The resulting osmotic imbalance would cause water to move into the dendrites, resulting in dendrite swelling and ultimately membrane disruption. Local application of the glutamate agonist AMPA induced a destruction of primary auditory dendrites similar to that observed after acoustic trauma, while the application of the glutamate antagonist kynurenate protected dendrites of the primary auditory neurons from noise-induced damage. The time course of the synaptic repair after acoustic trauma corresponded with the recovery of the auditory threshold (262, 264).

Threshold shifts may be modulated in several ways. Simultaneous acoustical stimulation with a tone of the same frequency delivered to the other ear may decrease the value of monaural TTS (36, 269, 271, 272). The TTS in guinea pigs evoked by a 10-kHz pure tone at 107 dB SPL for 1 min decreased by ~30% by simultaneous exposure of the other ear to a 10-kHz pure tone at 85 dB SPL. When the other ear is stimulated with a different frequency, the reduction in TTS does not occur. The reduction in TTS is mediated by the activation of the descending olivocochlear bundle and usually is demonstrated by a suppression of otoacoustic emissions elicited by stimulation of the contralateral ear (258, for review, see Ref. 174). Another type of modulation or suppression of threshold shifts is represented by the conditioning or toughening procedure. The procedure is based on experimental results (269, 270) showing that an initial monaural low-level sound exposure could significantly reduce the threshold shift caused by a subsequent high-level loud sound exposure to the same cochlea, even when there was no residual TTS to the priming sound. Later it was shown (31) that protection against noise trauma can occur when guinea pigs are sound conditioned to a continuous low-level, long-term, nondamaging stimulus before the traumatizing exposure. Sound conditioning provides significant protection against the traumatizing stimulus compared with a control, unconditioned group. Another way of providing protection against noise trauma is by using interrupted repetitive stimulation.

Mechanisms put forth to explain the conditioning phenomenon include a decrease in calbindin in the cochlea (30), increases in heat shock proteins in the cochlea (6), changes in the cochlear antioxidant activity (117), and the effects of cochlear efferents on the hair cells. For example, in chinchillas exposed to a conditioning paradigm, protection of the hair cells in the organ of Corti from noise-induced damage was associated with increased levels of antioxidants in the stria vascularis (117). The role of cochlear efferents in acquired resistance to noise-induced hearing loss is less clear. Complete deefferentation of the ear, i.e., transection of both crossed and uncrossed fibers of the olivocochlear bundle, in chinchillas exposed to noise after a conditioning paradigm revealed substantially more TTS, greater PTS, and larger cochlear lesions in the OHC in the deefferented ears (404). The results of experiments in conditioned guinea pigs (154) confirmed a larger PTS in animals after deefferentation; however, the authors found that animals undergoing sham surgery (brain stem cuts that failed to transect the crossed olivocochlear bundle) appeared protected whether or not they received the conditioning noise exposure. Conditioning-related protection may arise from a generalized stress response, rather than from the function of the olivocochlear bundle (154). The protection afforded by conditioning may not be completely explained by amplification of the olivocochlear reflex but rather by a general enhancement of cochlear sensitivity (155).

B. Changes in the Central Auditory System

Hair cell loss in the cochlea after auditory overstimulation is connected with the degeneration of auditory nerve fibers. Patterns of axonal degeneration were found in the brain stem of adult chinchillas (140, 222). The pattern of terminal degeneration in the ventral cochlear nucleus correlates with the position of IHC loss in the cochlea, i.e., it is cochleotopic. This process is consistent with the dystrophy resulting from the disappearence of IHC and auditory nerve fibers. However, in addition to the dystrophic process (present mostly in the ventral cochlear nucleus), fine fiber degeneration occurs without expressed cochleotopic correlation in the dorsal cochlear nucleus and *trans*-synaptically in the superior olive and IC. It is possible that an excitotoxic process, similar to that described at the synapses between IHC and auditory nerve fibers, plays a role in this type of terminal degeneration.

The effects of noise exposure on the central auditory system depend on the intensity, frequency content, and duration of the exposure. Differences may also be present immediately after exposure or at later time periods. The characteristic consequences of peripheral sensorineural hearing loss resulting from noise exposure are threshold shifts, abnormally rapid loudness growth, poor speech discrimination, and a reduction in the temporal summation of acoustic energy. Threshold shifts correspond with the degree of hair cell dysfunction in the inner ear (either temporary or permanent) and may be detected by any type of gross auditory evoked potentials (usually brain stem-evoked potentials or middle latency responses) as a shift in the potential threshold. Similarly, threshold shifts are reflected in shifts of the tips of tuning curves to higher intensities (22, 98, 170, 256, 359). Neuronal threshold shifts have been reported to be different at different levels of the auditory pathway with higher shifts present in neurons of the IC than in neurons of the cochlear nucleus (CN) in the same animal (293, 331). These findings did not receive further experimental support, but significant differences between auditory nuclei were found in response to suprathreshold sounds. In contrast to the situation in the auditory nerve and cochlear nucleus, the amplitudes of evoked responses in the IC (19, 294) and in the auditory cortex (257, 334, 335) were found to be enhanced compared with the preexposure situation (Fig. 4). The enhancement was observed immediately after noise exposure and lasted for many hours or days. The intensity of sound exposure must be >105 dB SPL. The recovery of the enhanced amplitudes to normal values exhibited a different time course than the recovery of threshold shifts (334, 335). Greater susceptibility to noise exposure, expressed as threshold shifts and enhanced amplitudes of cortical evoked potentials, was found in rat pups during the first 6 wk after birth (287).

It is possible to explain the enhanced amplitude of evoked responses in the IC and AC by the lack of inhibition in these structures after exposure. This idea was supported by the results of experiments in which neurons were recorded in the CN (22) and in the IC (359) before and after exposure to high-intensity pure tones, the frequency of which was just above the neuron's CF. If a unit had an inhibitory response area at frequencies above the CF and if the traumatizing tone reduced the magnitude of the inhibitory response, then the neuron's discharge rate to suprathreshold tones at the CF increased (Fig. 5).

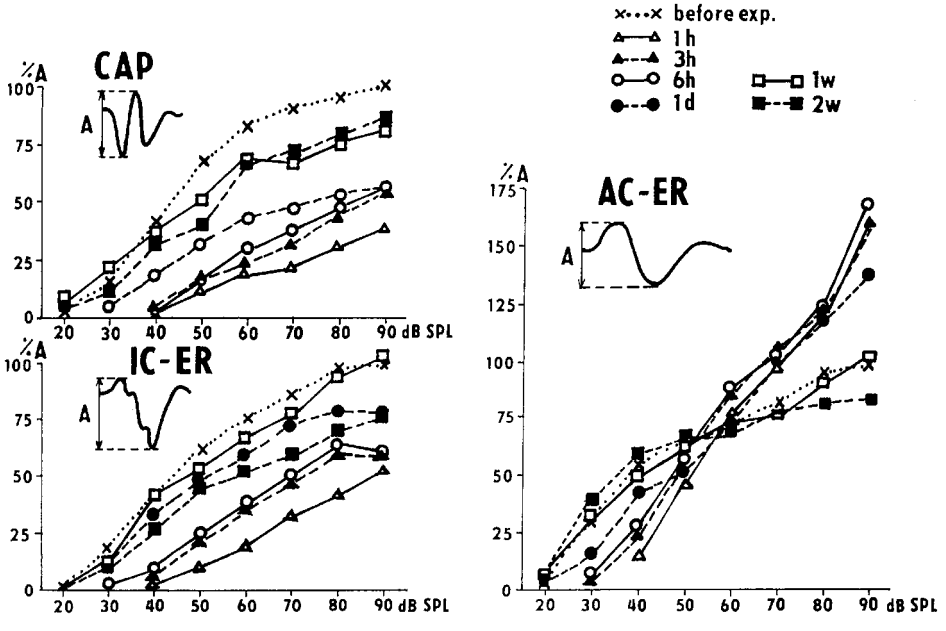

FIG. 4. Average amplitude-intensity functions for the auditory nerve action potential (CAP), evoked responses in the inferior colliculus (IC-ER), and evoked responses in the auditory cortex (AC-ER) measured before noise exposure and at different times after exposure. The ordinate expresses the potential amplitude in percentage of the amplitude measured at 90 dB SPL before exposure (A). *Inset*: principle of amplitude measurement. [From Popelář et al. (257).]

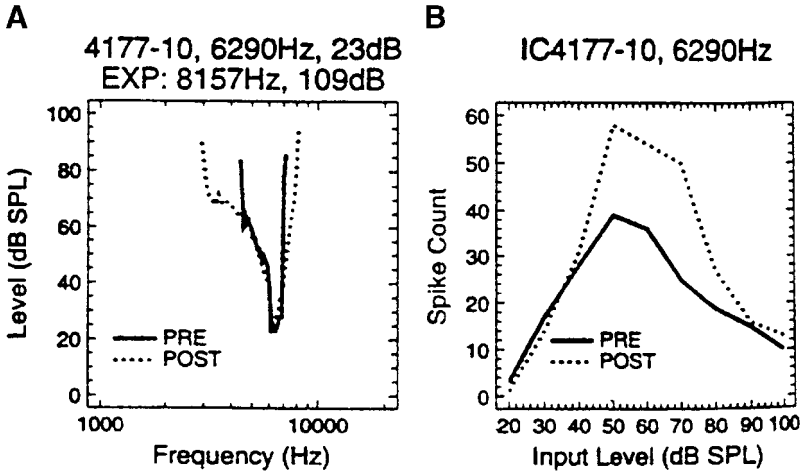

FIG. 5. Preexposure and postexposure tuning curves (*A*) and discharge rate level functions at the CF (*B*) of a neuron from the central nucleus of the inferior colliculus. CF, CF threshold and exposure conditions shown at *top* of panel. [From Wang et al. (359).]

Similar to the case of exposure to wide band noise (331), the exposure to a pure tone at a frequency just above the CF did not change the shape of the poststimulus time histogram, i.e., the pattern of the unit response (22, 292, 295, 296, 359). The discharge rate increased particularly in those neurons that had nonmonotonic rate-level functions, i.e., in neurons where the inhibitory influence was large at high sound intensities. Decreased inhibition after noise exposure was also found in other studies. For example, a decreased influence of the GABA antagonist bicuculline on one part of the IC evoked response was noticed after noise exposure (336). Decreased levels of glutamate decarboxylase (GAD) isoforms were found in the rat IC 2–30 days after exposure producing 20–30 dB TTS and some limited PTS (1). Surprisingly, immediately after exposure, the levels of GAD were elevated compared with IC levels in normal animals. It has to be mentioned at this point that the decrease of inhibition in the cortex of experimental animals is a general phenomenon accompanying a loss of receptors in the periphery, not only in the auditory system but also in other sensory systems (see sect. II*B2*).

One of the changes that can be observed after noise exposure is a change in the frequency tuning of neurons. When exposure was to a tone above the CF and the neuron had inhibitory sidebands flanking the excitatory area (292, 296, 359), the low frequency area around the tail of the tuning curve expanded and in some cases the high-frequency excitatory area expanded as well. Changes in the frequncy tuning were not observed in the IC neurons with tuning curves that had extended low-frequency tails, a lack of inhibitory side bands, and monotonic spike-intensity functions.

The spontaneous activity of auditory nerve fibers and neurons in the central auditory system decreases after noise exposure as a rule (137, 291). An exception was an increase observed in units of the cochlear nucleus in the rhesus monkey after exposure to short-lasting tones of moderate intensity (173). Specific changes are present in the auditory cortex of the cat after 30-min exposure to a loud tone (93–123 dB); spontaneous activity increases significantly in the primary auditory cortex (AI), does not change in the anterior auditory field (AAF), and decreases in the secondary auditory cortex (AII) (141). Also, other parameters of neuronal function are affected to a different extent in different cortical fields: the mean threshold at the CF increases significantly in the AI and AAF but not in the AII, the mean frequency-tuning curve bandwidth decreases significantly in the AII, whereas an enhancement of frequency response areas around the CF is present most frequently in the AAF. These results, along with the results of others (28, 256, 257, 331, 334, 335), strongly suggest that the function of the auditory cortex is seriously disturbed after noise exposure.

Psychoacoustical experiments and behavioral experiments in animals have shown that acoustic overstimulation leads to a breakdown in temporal integration so that hearing-impaired listeners show relatively little improvement in threshold with increasing stimulus duration (315). In normal subjects, the threshold to a long-duration tone is ~12 dB lower than to a short-duration tone. In noise-exposed subjects, the extent of improvement with increased duration declines (122, 207, 399). No change was found in temporal integration in guinea pigs exposed to noise-producing asymptotic threshold shifts (330); however, the threshold shifts were relatively mild. Another type of function, frequently studied in experiments with temporal integration, the gap function (i.e., recognition of a silent period in a long duration acoustical stimulus), was also found to deteriorate after noise exposure. Gap thresholds increased in experiments with noise-exposed chinchillas only when the asymptotic threshold shifts exceeded 40 dB (77). In patients with sensorineural hearing loss, the gap resolution was found to be significantly poorer than in normal listeners (65, 78). Larger gap thresholds tended to be associated with slow rates of

recovery from forward masking. Similarly in experimental animals, increased time constants fitting forward masking data were found (9).

C. Tinnitus as a Central Phenomenon

Up to 15% of the world's population frequently or permanently suffers from subjective tinnitus, which is a phantom auditory perception without a counterpart in the outside world (105). A frequent cause of tinnitus is noise exposure and presbycusis, but tinnitus may appear as a side effect of treatment with ototoxic drugs (e.g., salicylates or chinin). There are several other mechanisms of tinnitus generation including involvement of the middle ear muscles, inner ear hydrops, etc. In many cases, however, tinnitus originates in the central auditory system or in brain structures related to the central auditory system. This statement is supported by the fact that tinnitus persists in patients with acoustic neurinoma after transection of the auditory nerve (107, 185). Recently, accumulated evidence from magnetoencephalography and positron emission tomography (PET) studies speaks in favor of a central origin for several types of tinnitus. In patients who could alter tinnitus loudness by performing voluntary oral facial movements, these loudness changes affected cerebral blood flow in the auditory cortex contralateral to the ear in which tinnitus was perceived, whereas unilateral cochlear stimulation caused bilateral effects (171, 172). Patients, compared with controls, showed evidence for more widespread activation by tones at aberrant links between the limbic and auditory systems. In a similar study (76), patients were used with another rare form of tinnitus elicited by eye movements. In this case the phantom auditory sensation increased regional blood flow bilaterally in temporoparietal association auditory areas but not in the primary auditory cortex. A marked shift of the cortical representation of the tinnitus frequency into an area adjacent to the expected tonotopic localization was observed with magnetoencephalography. The subjective strength of the tinnitus was found in this case to correlate strongly with the amount of cortical reorganization (224). The data obtained in patients with tinnitus thus confirmed the results of experiments in animals with partial cochlear lesion (see sect. II) and suggested that tinnitus in many cases is related to plastic changes in the auditory cortex and may be compared with phantom limb pain occurring after amputation. In patients with tinnitus, a slight shortening of the latency of the wave V in brain stem-evoked audiometry was also observed (209), as well as changes in N1-P2 latency of late auditory evoked responses (235) and changes in the modified contingent-negative variation paradigm (105).

Several other facts, known from clinics as well as from laboratory experiments, support the hypothesis of a central origin of tinnitus. Tinnitus can be suppressed in a large proportion of patients by electrical stimulation of the inner ear by temporary adjusted electrodes (94, 156) or in patients with cochlear implants (for review, see Refs. 349, 350). Some methods, borrowed from clinical and experimental psychology, such as cognitive behavior modification (326) or habituation (119), are successfully used in a treatment of tinnitus.

As an experimental animal model of tinnitus, an overdose of salicylate is usually used (62), which is known to induce tinnitus in humans. Large doses of salicylate (e.g., aspirin) are known to cause tinnitus in normally hearing individuals when blood concentration exceeds 250–450 mg/l (210). The tinnitus in this case precedes or occurs simultaneously with a hearing loss of 20–40 dB across the audible frequency range. The hearing loss and tinnitus are reversible within ~24–72 h of the cessation of salicylate administration. In cats injected intravenously with salicylate to induce similar blood level concentrations as in humans, increases in the threshold of responses to tones in auditory nerve fibers were found as well as increases in their spontaneous discharge rate (62). A similar increase in neuronal spontaneous activity was observed in the IC of guinea pigs after treatment with salicylate (120). An increased spontaneous activity was also found in the dorsal cochlear nucleus in hamsters after exposure to intense sound, which was, however, apparent only 1–2 mo after exposure (133). The authors suggested this type of hyperactivity after noise exposure be considered as an alternative animal model of tinnitus (131, 134).

The salicylate-induced model of tinnitus was recently used in gerbils; the activation of different parts of the central auditory system was studied with autoradiography of 2-[^{14}C]deoxyglucose (357) and with c-*fos* immunoreactivity (356). In contrast to the results obtained in guinea pigs (120), in gerbils salicylate treatment reduced activity in the IC, particularly in its high-frequency part, whereas elevated activation along some isofrequency contours was present in the auditory cortex. No differences in c-*fos* expression were found between salicylate-treated animals and controls in cochlear nuclei, nuclei of the lateral lemniscus, and the IC, but a pronounced accumulation of immunoreactive cells was found in areas susceptible to stress, in the locus coeruleus, the midbrain periaqueductal gray, and the lateral parabrachial nucleus in salicylate-treated gerbils. Similarly, as in the case of PET studies in humans (171), these results point to the involvement of some extra-auditory structures of the brain in the generation of tinnitus. Experimental data obtained in animals injected with salicylate either intravenously or intraperitoneally must, however, be interpreted with caution, since the doses of salicylate used in these experiments are unusually high (200–400 mg/kg by volume) and do not correspond with the doses normally used in the treatment of patients.

IV. EXPERIENCE-DEPENDENT PLASTICITY IN THE CENTRAL AUDITORY SYSTEM

A. Changes in Receptive Fields and Other Characteristics of Neuronal Responses

Several studies in the 1960s and 1970s demonstrated that single and multiple unit activity in the auditory cortex may be systematically modified during the acquisition of a tone-signaled task (25, 49, 237, 238). For example, Kraus and Disterhoft (150) observed changes in the single unit activity in the rabbit auditory association cortex throughout the acquisition of a classically conditioned, nicticating membrane response. Response plasticity most commonly manifested as an increase or decrease in the conditioned stimulus-evoked firing rate with little change in the response pattern as indicated by peristimulus histogram shape. However, a rapidly growing literature during the last 20 years has attested to a very extensive short- and long-term modification of receptive fields and a reorganization of representational maps, particularly in the cortex, elicited by learning, sensory stimulation, and sensory deafferentation (129, 366, 369).

An important step in understanding plastic changes in the auditory cortex during learning was initiated by Diamond and Weinberger (47), who investigated changes in the receptive fields (RFs) of single units in secondary and ventral ectosylvian auditory cortical fields in an immobilized cat during classical conditioning. In these areas, the cells usually showed a general increase in responses across the frequency domain after sensitization trials, whereas they exhibited either selective increases or selective decreases after associative learning. Associative changes in frequency RFs of most cells were specific to the frequency of the conditioned stimulus (CS), were established rapidly, and were reversed by extinction. Frequency RFs from single neurons were obtained before and after conditioning with a single tone. Posttraining RFs showed a systematic change in tuning, e.g., responses to the frequency of the CS were increased, whereas responses to other frequencies were decreased. Later, Weinberger's team used awake guinea pigs as an animal model for the study of RF plasticity. Single and multiple units were recorded from the primary auditory cortex, and as an unconditioned stimulus (US), the animal received a constant-current foot-shock through the chamber's grid floor (12, 14). This series of experiments showed that the effects in the guinea pig primary cortex were similar to those observed in the cat. Conditioning with a tonal CS produced a systematic change in the frequency RFs, with increased responses to the frequency of the CS and decreased responses to the preconditioned best frequency and many other frequencies. Thus classical conditioning enhanced the processing of the CS frequency compared with other frequencies. The CS-specific RF plasticity was possible to elicit only by associative learning and not by sensitization (i.e., by presentation of an acoustical stimulus unpaired with a US). The conditioning evoked increases in the firing of a single unit were highly specific to the CS and were not possible to evoke at frequencies only 0.1 octaves away from the CS frequency (59). Receptive field plasticity developed as rapidly as the behavioral signs of conditional fear, after only five training trials (55), and was enduring, as seen by within-subject recordings obtained before and at weekly intervals for up to 8 wk after conditioning (370). In the latter study, subjects were trained while awake, but RFs were obtained while they were anesthetized. Changes in cortical RFs were also observed in alert Mongolian gerbils during differential frequency conditioning (236). A reinforced CS, which was paired with electrocutaneous stimulation as US, produced specific changes such that the reinforced frequency became located in a local minimum of the RF after training. This resulted from a training-induced increase in the responses to frequencies adjacent to the reinforced frequency in the RF (these frequencies were presented during training without pairing with an electrocutaneous stimulation). Changes induced by conditioning were stable under retention training and gradually disappeared during extinction training.

Early in the above-mentioned experimental series questions arose concerning the involvement of subcortical structures in conditioning-elicited RF plasticity. Only short-term effects were detected after associative training in the primary lemniscal ventral division of the MGB: selective effects were present immediately after training, but they dissipated when RF was tested 1 h after training (57). Specific retuning occurred only if the CS frequency was within one-eighth of an octave from the pretraining best frequency (BF). In contrast to this, in other nonlemniscal MGB divisions, the medial and dorsal divisions, the effects observed after associative training shared many characteristics with the effects described at the cortical level. Selective CS-specific effects were found in 55 and 48% of the neurons in the dorsal and medial divisions, respectively. In these two divisions, the effects were sustained and were sometimes more selective when the RF was tested 1 h after training (56, 58). Heterosynaptic long-term facilitation of the auditory cortex by the magnocellular medial geniculate body has a role in the model of learning-induced receptive field plasticity proposed by Weinberger and Bakin (369). According to this model, the medial division of the MGB promotes RF plasticity in the auditory cortex via its synapses in layer I on the apical dendrites of pyramidal cells. The hypothesis is based on results of experiments in guinea pigs. Modification of evoked activity in the auditory cortex was found when electrical stimulation of the medial MGB was paired with preceding clicks in adult animals under barbiturate anes-

thesia (371). The amplitudes of averaged click-evoked potentials were significantly elevated compared with sham-stimulated controls.

Modulation induced by acetylcholine plays an important role in the learning-induced RF plasticity model proposed by Weinberger and Bakin (369). Activation of the cholinergic system can modulate RF tuning either in an associative manner or as a potential response to a shift in the behavioral state. The major subcortical source of cortical acetylcholine is the nucleus basalis (NB) (88, 124, 125, 162, 195). Cholinergic projections from the NB to the auditory cortex have been hypothesized to be involved in learning-induced RF plasticity in the auditory cortex (367, 368). Several arguments support this hypothesis: a blockade of the central cholinergic system impairs learning, particularly that involving the forebrain (46, 190), and a NB-elicited release of acetylcholine in the cerebral cortex is necessary to shift the electroencephalogram (EEG) from the synchronized (high-voltage slow waves) to the desynchronized (low-voltage fast waves) pattern that characterizes the waking state (26, 191, 198). The neuromodulatory actions of acetylcholine have been implicated in sensory cortical plasticity in adults (398). Furthermore, the iontophoretic application of muscarinic agonists (191) or anticholinesterases (10) produced a lasting modification of frequency tuning. Stimulation of the NB produced an atropine-sensitive lasting modification of evoked responses in the auditory cortex, including facilitation of field potentials, cellular discharges and excitatory postsynaptic potentials evoked by stimulation of the MGB (196, 197). In addition, NB stimulation paired with a tone was found to induce a facilitation of evoked responses in the ipsilateral auditory cortex in rat (53), which was possible to block with atropine (54). Pairing a tone with the iontophoretic application of muscarinic agonists produced pairing-specific, atropine-sensitive modification of RFs that included tuning shifts to or toward the frequency of the paired tone (199). Later it was found that pairing a tone with stimulation of the NB can induce RF plasticity in the auditory cortex in urethan-anesthetized guinea pigs (15). The effects remained 30 min after pairing, the longest interval tested, and they were found to be associative because a sensitization control failed to produce RF plasticity. These effects were also observed in awake guinea pigs in which stimulation of the basal forebrain was accompanied by a single tone (16) or by two tones in a discriminative test. RFs from neuronal discharges before and after differential pairing revealed the induction of the predicted plasticity, as well as increased responses to the paired tone and decreased responses to the unpaired tone. RF plasticity in awake guinea pigs was also induced during instrumental avoidance conditioning (13). Classical (Pavlovian) conditioning to a tone followed by a shock resulted in fear conditioning to the tone. In contrast to this, instrumental avoidance conditioning prevented full elicitation of fear by the CS. This result showed that long-term RF plasticity does not require continual evocation of fear.

The RF plasticity discussed so far was observed in evoked potentials, single units, or multiple units in the auditory cortex or MGB; however, the main interest was always in the changes over time during conditioning or NB stimulation. In contrast, experimental studies showing the effects of deafferentation (see sect. II) demonstrated reorganization in the projection areas of the auditory cortex. Kilgard and Merzenich (138) combined both approaches when investigating the effects of prolonged pairing of tonal stimulation with electrical stimulation of the NB on the auditory cortex tonotopic map in rats. Unanesthetized and unrestrained rats were stimulated by a tone paired with NB stimulation occurring randomly every 8–40 s. Paring was repeated 300–500 times/day for 20–25 days. The animals were anesthetized, and a detailed map of the primary auditory cortex was generated from 70–110 microelectrode penetrations. The training procedure resulted in a significant reorganization of the tonotopic cortical maps compared with maps in control untrained animals, with expanded representation of the frequency corresponding with the stimulation tone. In some animals the expansion was connected with a decrease in the representation of frequencies lower than the stimulation tone; in others the decrease was seen at higher frequencies. The authors suggest that this type of differential plasticity parallels the receptive field remodeling that results from different types of behavioral training. The results also demonstrate that input characteristics may be able to drive appropriate alterations of receptive fields independently of explicit knowledge of the task. The results of experiments pairing tone stimulation with electrical stimulation of the NB were similar to those performed in adult owl monkeys using dicrimination training (279). In monkeys trained for several weeks to discriminate between small differences in the frequency of sequentially presented tonal stimuli, the tonotopic organization of the AI was studied by recording multiple-unit responses. The cortical representation and the sharpness of tuning were greater for the behaviorally relevant frequencies of trained monkeys compared with the same frequencies of control monkeys. Pairing of the acoustical stimulation with electrical stimulation of the NB also resulted in plastic changes in temporal information processing in the primary auditory cortex of the rat (139). While in untrained rats neurons in the primary auditory cortex could not respond to tone sequences faster than 12 pulses/s, in rats trained with NB stimulation paired with 15 acoustical pulses/s, the following rate significantly increased. Moreover, pairing NB stimulation with 5 pulses/s markedly decreased the cortical response to rapidly presented stimuli. Apparently, NB stimulation paired with different acoustical stimuli is able, through its

cholinergic input to the auditory cortex, to shape many parameters of the firing of cortical neurons.

In the model of RF plasticity in the auditory cortex proposed by Weinberger and co-workers (367, 368) and later by Weinberger and Bakin (369), the specificity of RF plasticity is dependent on Hebbian rules of covariance (Fig. 6). Two modified Hebbian rules were invoked in the model to explain increased responses to the CS frequency and decreased responses to non-CS frequencies. *1*) If a presynaptic input and the postsynaptic cell are both active at the same time, then synaptic strength is increased. *2*) If the presynaptic input is not active but the postsynaptic cell is active, then synaptic strength is weakened. Active refers to a state of increased excitability and not necessarily to cellular discharges. The experimental verification of the hypothesis was performed in urethan-anesthetized adult guinea pigs (41). During the covariance treatment, one tone was paired with an excitatory juxtacellular current, applied to a single postsynaptic cell in the primary auditory cortex. Excitatory current increased postsynaptic discharge, thereby increasing covariance between the activity of the postsynaptic cell and its afferents that were activated by the tone. Within the same cell a second, different tone was paired with an inhibitory juxtacellular current, decreasing covariance between the postsynaptic cell and the afferent activated by the second tone. After treatment, responses to tones associated with increased covariance strengthened significantly relative to tones associated with decreased covariance, as predicted by the Hebbian hypothesis. This occurred in 32% of cells undergoing 120 pairing trials, but in only 11% of cells undergoing 60 trials. Significant plasticity lasted more than 15 min. The probability of plasticity was significantly higher when the cortical EEG was desynchronized during treatment than when synchronized. The involvement of Hebbian rules in cortical RF plasticity is, however, not uniformly accepted. For example, Edeline (52) summarized arguments against the general acceptance of these rules in auditory cortex RF plasticity and suggested looking for other possible explanations for RF plasticity.

Plastic changes in the firing of cortical units were also induced by intracortical microstimulation (ICMS). Originally this method was used in the somatosensory cortex in the rat (48) and later extended to study the rat auditory cortex (180, 181). In the first case, the extent of correlated spontaneous activity in neuronal pairs after several hours of ICMS was enlarged severalfold; in the case of the auditory cortex, the ICMS enhanced highly

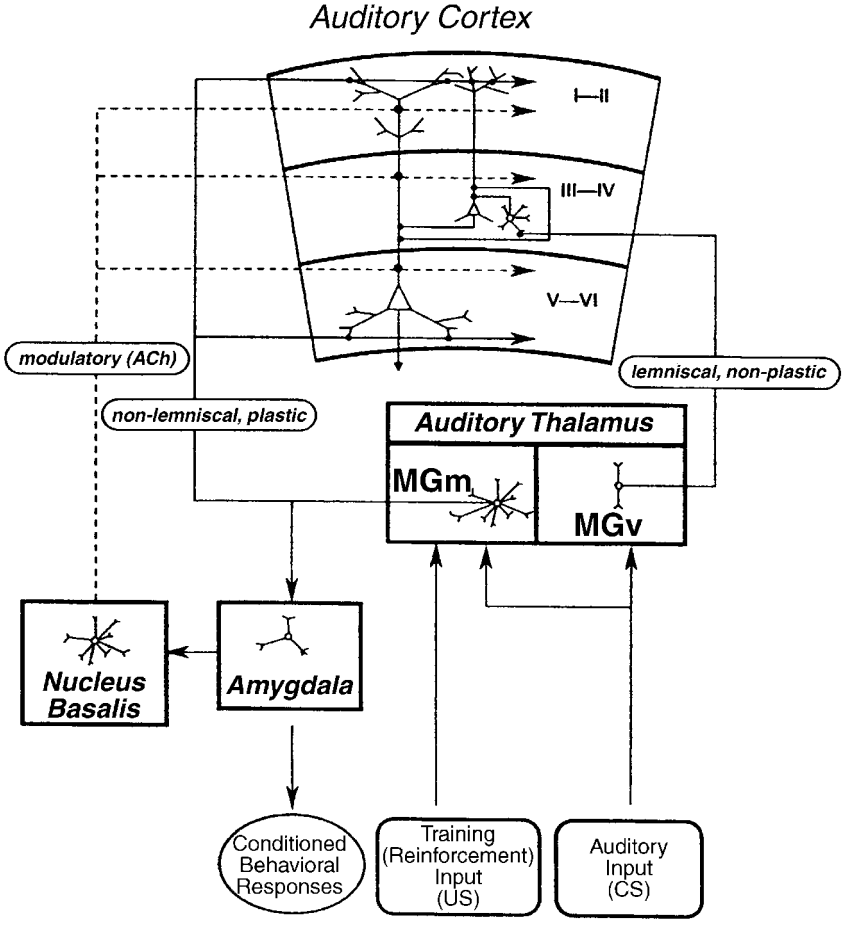

FIG. 6. Schematic model of the anatomic projections of the three systems that act synergistically within the auditory cortex (ACx) to produce and maintain condition-specific receptive field plasticity and conditioned behavior. Together the three systems *1*) provide detailed frequency information to the auditory cortex [via the lemniscal nonplastic pathway originating in the ventral part of the medial geniculate body (MGv)], *2*) indicate the behavioral significance of the acoustic stimulus [via the nonlemniscal pathway originating in the medial part of the medial geniculate body (MGm)], and *3*) produce neuromodulation proportional to the importance of the auditory stimulus [by the modulatory cholinergic projection from the nucleus basalis (NB)]. Auditory and nonauditory inputs converge in the auditory thalamus. Learning produces increased responses in the MGm, which are projected to the NB and the ACx. Increased cholinergic release in the ACx, combined with increased synaptic drive from the auditory thalamus, produces long-lasting plasticity in the ACx. [From Weinberger and Bakin (369).]

synchronous oscillatory patterns induced by acoustical stimulation. Furthermore, an enlargement of the cortical domain tuned to the acoustical frequency that had been represented at the stimulating electrode was found in the auditory cortex. Evaluating the changes in functional interactions between adjacent neurons was used as an approach to investigating the mechanisms of cortical plasticity in behaving monkeys (4). The effect of a single neuron on another neuron was evaluated by cross-correlating the firing times of the two neurons. When two neurons were induced to fire together within a short time window, the functional connection between them was potentiated, and when simultaneous firing was prevented, the connection was depressed. These modifications were strongly dependent on the behavioral context of the stimuli that induced them.

In another approach, the RF plasticity was studied in unanesthetized guinea pigs before, during, and after iontophoretic application of norepinephrine (182). Similar to the application of GABA, norepinephrine application resulted in a significant inhibition of spontaneous and tone-evoked activity and in a decrease in the size of the receptive fields. Metabolic changes associated with conditioning were also studied with the aid of the 2-deoxyglucose method (79, 80). The experiments involved freely behaving rats in a Pavlovian conditioning paradigm in which a 4- to 5-kHz frequency-modulated tone (CS) was paired with aversive electrical stimulation of the midbrain reticular formation (US). The unconditioned response was a rapid decrease in heart rate. The results showed that within each auditory nucleus as well as within the auditory cortex, a region of overlap of the spatial representation of the conditioned and unconditioned stimuli developed an enhanced metabolic response during conditioning.

Auditory conditioning (associative learning) was found to induce reorganization of the frequency maps of the AI and the IC in the big brown bat (*Eptesicus fuscus*) (70, 289). During the conditioning procedure, acoustic stimuli were followed by electric-leg stimulation. The resulting effects were shifts in the frequency-tuning curves and the best frequencies of collicular and cortical neurons. Inactivation of the primary auditory cortex during conditioning abolished these collicular changes. Therefore, the corticofugal descending auditory pathway must be involved in the plasticity of the IC. Focal electrical stimulation of the AI evoked the same changes in the IC and AI as those evoked by auditory conditioning. It was possible to augment the best frequency shifts, expressed as changes in the cochleotopic maps, by electrical stimulation of the basal forebrain (178) or by acetylcholine applied to the AI (123). These results correspond with the previously described examples of experience-dependent plasticity in the central auditory system and extend the mechanisms of plasticity by involving the activity of the corticotectal descending pathway.

B. Experience-Dependent Plasticity in Humans Including Remediation of Language Learning Impairment

Experience-dependent plasticity of the auditory cortex was also recently demonstrated in humans with PET (223) and magnetoencephalography (243, 244). Conditioning-related, frequency-specific modulation of tonotopic neural responses was observed in the auditory cortex of subjects during discriminatory classical conditioning of high- or low-frequency tones by an aversive white noise burst (223). The modulated regions of the auditory cortex positively covaried with activity in the amygdala, basal forebrain, and orbitofrontal cortex and showed context-specific functional interactions with the medial geniculate body. Short-term plasticity, similar to that observed in the ferret (216), was demonstrated in the human auditory cortex by magnetoencephalographic measurements (244). Subjects listened for 3 h on 3 consecutive days to music "notched" by the removal of a narrow frequency band centered on 1 kHz. Immediately after listening to the notched music, the neural representation for a 1-kHz test stimulus centered on the notch was found to be significantly diminished compared with the neural representation for a 0.5-kHz control stimulus centered one octave below the region of notching. The diminished neural representation for 1 kHz reversed to baseline between successive listening sessions. The short-term plasticity was also demonstrated in a study of the neurophysiological correlate of the auditory after-image, so-called "Zwicker tone" (104). This is an auditory after-image that can be evoked most effectively when a band-suppressed noise presented for a certain period of time has been switched off. The sensation of this phenomenon is that of a pure tone with a frequency corresponding to the center frequency of the noise gap. A sustained neuromagnetic activity was observed in the supratemporal auditory cortex that accompanied this sensation. In contrast to the sustained activity, which is due to an external acoustical stimulus, the sustained activity associated with the Zwicker tone seems to result from a temporary reduction of neural activity originating from those regions in which the Zwicker-tone exciting stimulus caused adaptation.

In addition to short-term plasticity, long-term plasticity has been confirmed in the human auditory cortex. Increased auditory cortical representation was observed in highly skilled musicians (243). Dipole moments for piano tones, but not for pure tones of similar fundamental frequency (matched in loudness), were found to be enlarged by ~25% in musicians compared with control subjects who had never played an instrument. Enlargement was correlated with the age at which musicians began to practice and did not differ between musicians with absolute and relative pitch. The comparison between the latter two groups was done because left-hemispheric enlarge-

ment of the planum temporale has been reported (299) to be more pronounced for musicians with absolute pitch than for musicians with relative pitch. Magnetoencephalographic measurements were able to demonstrate plastic changes in the somatosensory system of musicians, since a modified cortical representation of the fingering digits was found in skilled violinists (61). In another simple and elegant demonstration of central auditory system plasticity in humans associated with speech discrimination training, an electroencephalographic test of mismatch negativity was used (151). Subjects were trained to differentiate two acoustically slightly different phonemes /da/, and during the training, differentiation ability was tested with mismatch negativity, i.e., a cortical evoked response appearing when a series of identical stimuli is suddenly disrupted with a different stimulus. The results demonstrated that listening training can change the neurophysiological responses of the central auditory system to just-perceptible differences in speech.

Much progress has been achieved recently in the practical utilization of knowledge of human brain plasticity in the treatment of language learning impairment (338). Accumulated evidence has shown that a dysfunction in normal phonological processing, which is critical to the development of oral and written language, may derive from difficulties in perceiving and producing basic sensory-motor information in rapid succession (340). The results of several studies gave evidence that the left hemisphere in humans is specialized for processing rapidly changing acoustic information, including, but not limited to, speech. Activation of the Brodmann area 45 in the frontal operculum was found to be affected by the rate of change of acoustic events, regardless of whether stimuli were verbal or nonverbal (63). The data led to the hypothesis that highly specific, intrinsic neural processing rates may have developed through evolution, with more rapid rates of processing apparently lateralized in the left hemisphere. On the basis of these mechanisms, fundamental processes known to underlie articulatory coding for speech production and perception later evolved. Results of studies conducted in animals and humans led to the hypothesis that training exercises used for neural plasticity studies in monkeys and rats might be adapted to alleviate the temporal integration deficits reported in children with language-based learning impairment (194, 339). Children with this impairment were trained with acoustically modified speech and adaptive computer games 2 h/day, 5 days/week for 4 wk. The results of the study demonstrated that adaptively training the acoustic-processing rate, coupled with language and phonological processing training, resulted in dramatic improvement in the temporal integration rate, phonological processing, and language comprehension abilities. On the basis of this laboratory study, a large field study was conducted in clinical and classroom settings that confirmed the laboratory data and started the successful application of this method in the treatment of language processing deficits in children.

Recently, the Merzenich and Tallal groups (3, 225) presented new evidence for a link between impaired auditory resolution and poor reading abilities. In adults with a childhood history of reading difficulties, deficits were found in psychoacoustic measures in which stimuli were presented in brief forms and in rapid succession (3). Similar results were obtained when adults with poor versus good reading abilities were tested with magnetoencephalography (225). The responses to rapid sequences of brief acoustical stimuli were substantially weaker in poor readers compared with controls. In dyslexic children, a functional magnetic resonance imaging (fMRI) study during phonological and orthographic tasks of rhyming and matching visually presented letter pairs demonstrated significant differences in the activation of cortical regions (342, 343). Dyslectics who participated in a remediation program showed increased activity in the left prefrontal cortex after training, which was normally activated in children without reading impairment.

VI. CONSEQUENCES OF DEAFNESS AND ELECTRICAL STIMULATION OF THE AUDITORY SYSTEM

A. Changes in the Structure and Function of the Central Auditory System in Animals After Deafening and Electrical Stimulation of the Cochlea

Several experimental approaches may be used to produce hearing loss of peripheral origin, i.e., destruction of sensory hair cells. Destruction of hair cells results from topical or systematic injection of ototoxic drugs such as aminoglycoside antibiotics and/or ethacrynic acid, from exposure to high-intensity noise, or from mechanical lesions. In all cases the loss of IHC is accompanied by a degeneration of spiral ganglion cells (SGC) and consequently auditory nerve fibers (128, 157, 204, 364, 402). The loss of spiral ganglion cells is progressive with ~50% of cells missing 9 wk after deafening a guinea pig by injection of an ototoxic drug, declining to 10% surviving cells 16 wk after deafness (128). Similar observations were made in the cat; 2.5 years after neonatal deafening only 17% of SGC survived compared with normal animals (84). The degree of SGC survival is correlated with the excitability of the auditory system. A reduction in the number of surviving SGC results in a reduction in the amplitudes of electrically evoked middle latency responses (128) and electrically evoked brain stem responses (82). Results of early experiments suggested that chronic electrical stimulation via cochlear implants is able to reduce the SGC

degeneration seen after aminoglycoside-induced hair cell loss, as measured by SGC densities in kittens (158, 160) and in guinea pigs (91, 175, 204). In animals chronically electrically stimulated via intracochlear electrodes, smaller reductions in the slope of input-output functions of electrically evoked brain stem responses (EABR) were observed over time than in nonstimulated animals, and in some cases, there was no change in input-output functions in stimulated animals at all (204). However, several other studies did not confirm the evidence of a SGC-sparing effect for electrical stimulation but did demonstrate increased SGC size in the stimulated ear (8, 306). Another possibility suggested to explain the increased density of SGC in the electrically stimulated ear is a narrower Rosenthal canal resulting from electrically induced bone growth (168). This finding does not support the hypothesis that chronic monopolar electrical intracochlear or extracochlear stimulation acts as a neurotrophic factor. The problems seem to be unresolved at the present time, since Leake et al. (159) were able to repeat their original experimental data in neonatally deafened cats with similar results, showing 50% of normal SGC density maintained in chronically stimulated ears, compared with 30% on the control deafened side. In addition, they found significantly larger cells in the stimulated ears in the regions with the greatest stimulation-induced differences in cell density.

While in the cochlea neonatal deafening produces a loss of SGC, in the cochlear nuclei of guinea pigs and kittens changes appear in the cell size. A sensorineural hearing loss results in a significant reduction in the size of neurons in the ipsilateral ventral cochlear nucleus (7, 92, 184, 211, 212, 259, 347); similar effects were observed following neonatal conductive hearing loss (37, 38, 361–363). After neonatal long-term deafening in the cat by neomycin, which resulted in hair cell destruction, there was a highly significant shrinkage of ~42% in total cochlear nucleus volume, a 38% reduction in mean spherical cell size, and a 57% decrease in spherical cell density in the anteroventral cochlear nucleus (AVCN), compared with the CN of the normal adult cat (176). A 46% reduction in total CN volume compared with normal animals was observed in neonatally deafened cats in another study (84). In adult guinea pigs 8 wk after lesioning of the cochlea by topical administration of the ototoxic antibiotic neomycin in the middle ear cavity, the average area of neuronal somata in the rostral AVCN on the lesioned side was 22% smaller than the average area of these cells on the normal hearing side (163, 204). The decrease in the size of neurons appeared only in animals with a loss of both OHC and IHC, whereas in animals with a loss of OHC only, the size of AVCN cells did not change. Studies with chronic electrical stimulation in neonatally deafened animals brought more conclusive results regarding the changes in the CN than studies investigating changes in the SGC. Kittens, systematically deafened binaurally using kanamycin and ethacrynic acid, received bilateral cochlear implants and were stimulated unilaterally for periods up to 4 mo (184). After this period of stimulation, the areas of the cell somata within the AVCN on the stimulated side were found to be significantly larger than those of corresponding somata on the control, unstimulated side. Similarly, in another study, neonatally deafened cats were stimulated daily with a scala tympani electrode array over a period of 3 mo, and the size of spherical cells in the AVCN ipsilateral to the stimulated cochlea was larger than on the unstimulated side (176). The prevention of shrinkage in cell size in the cochlear nucleus was also observed in deafened guinea pigs that were stimulated for several weeks by an electrical current through implanted electrodes in the cochlea (204). However, the effects were observed only with 200-μA currents and not with 100-μA currents. Unilateral electrical stimulation through electrodes implanted in the cochlea did not produce any changes in the size of cochlear nucleus neurons in normal hearing kittens (230) compared with the unstimulated side. In normal animals without hair cell loss, electrical stimulation of the inner ear produces excitation not only of auditory nerve fibers but also of hair cells (186, 332).

The effects of cochlear ablation and the amelioration of the negative effects of such cochlear ablation with the aid of electrical stimulation of auditory nerve fibers were also studied at the level of the midbrain. Snyder et al. (313, 314) have shown that chronic electrical stimulation of the auditory nerve fibers in the neonatally deafened cat results in changes in the functional properties of neurons in the IC. They compared the response properties of neurons in the IC in cats neonatally deafened and stimulated for up to 3 mo through electrodes implanted in the cochlea with responses in a group of cats neonatally deafened and unstimulated and with healthy controls. They found that the tonotopic arrangement of the IC does not change in neonatally deafened animals; however, the sector activated by electrical stimulation in the IC was significantly larger in chronically stimulated animals compared with the other two groups. Furthermore, they observed that units in the IC respond to electrical stimulation with significantly shorter latencies, their late response latencies are significantly longer, and the frequency of occurrence of inhibitory and late responses is significantly higher. An improvement in the temporal resolution of neurons in the IC was reported in cats neonatally deafened and stimulated electrically for several months (312). Neurons in such cases phase-locked to higher stimulus frequencies than those in either normal or neonatally deafened and unstimulated animals. The temporal resolution of IC neurons in neonatally deafened cats, investigated 1 yr after deafening, was found to be significantly reduced in cases of bilateral deafening compared with acutely deafened animals (305). Also, the spontaneous

activity of IC neurons was higher in deafened animals than in controls. However, neonatally unilaterally deafened animals showed no reduction in temporal resolution. Apparently, monaural afferent input is sufficient to maintain normal levels of temporal resolution in auditory midbrain neurons. This finding corresponds with the fact that the synaptic density in the IC in cats neonatally deafened in both ears is significantly lower than the density in normal hearing animals and unilaterally deaf animals (83) and also with the finding that the soma area in neurons of the central nucleus in bilaterally deafened cats is reduced compared with normal hearing controls and unilaterally deafened cats (233). The IC must not be considered necessarily as a homogeneous structure, since neurons in its lemniscal part, the central nucleus, respond to acoustical stimuli in a different way than those in the extralemniscal part, the dorsal and external cortices (333). Similarly, neurons in the lateral nucleus (i.e., external cortex) exhibit longer latencies to electrical stimulation of the cochlea than neurons in the central nucleus (305). The effects of electrical stimulation of the auditory nerve fibers on IC activity may be dependent on the animal species and the time interval between deafening and the recording of IC responses. In rats and guinea pigs (18, 17), investigated 21 days after deafening, there was no difference between spontaneous activity in normal control animals and deaf animals and no difference in the thresholds of units to 100-Hz sinusoidal electrical stimulation of the auditory nerve fibers. A significant reduction was found, however, in the number of IC units suppressed by electrical stimulation of the contralateral ear in normal animals (42%) and in deafened animals (5%). Unfortunately, normal control rats and guinea pigs were investigated without deafening. The level of electrically evoked inhibition in the IC of deaf cats as well as in normal controls was low (305).

Changes in the central auditory system after cochlear ablation were also observed in transmitter release and uptake and in the expression of GABA, glycine, and *N*-methyl-D-aspartate (NMDA) receptors. In young adult guinea pigs, transient as well as permanent changes in GABA and glycine release and uptake in different auditory brain stem nuclei were observed during a period of 145 days after unilateral cochlear ablation (320). For example, [^{14}C]glycine uptake was elevated bilaterally in the cochlear nucleus and medial superior olive, whereas [^{14}C]GABA uptake was depressed bilaterally in the auditory midbrain. Glycinergic inhibition, studied with [^{3}H]strychnine binding, was persistently weakened ipsilaterally in the ventral cochlear nucleus and the lateral superior olive and bilaterally in the dorsal cochlear nucleus, whereas it was strengthened in the contralateral lateral superior olive (321). Unilateral cochlear ablation produced only transient changes in the expression of NMDAR1 isoforms in the rat superior olivary complex that disappeared 20 days after deafening (228). In support of the electrophysiological data (see above), the results of in vivo microdialysis in guinea pigs revealed that the potassium-stimulated release of GABA from the central nucleus of the IC was markedly suppressed in animals deafened for 30 days (17, 18). This finding suggests that hearing loss induces a downregulation of inhibition in the IC and is proposed as a reason for the fact that after deafening in the rat, there is an increase in the number of Fos-immunoreactive neurons in the IC evoked by contralateral cochlear electrical stimulation compared with normal animals (17, 18).

The experiments with 2-deoxyglucose uptake in deafened guinea pigs demonstrate that 9 wk after deafening, the metabolic rate in the IC is reduced; however, the reduction may be reversed in animals that receive continuous electrical stimulation of the inner ear (204). The reversal of degenerative changes in the central auditory system may be produced not only by chronic electrical stimulation of the auditory nerve fibers, but also by direct application of neurotrophic factors in the inner ear (5, 205). Two weeks of treatment with brain-derived neurotrophic factor (BDNF) administered chronically via a miniosmotic pump into the scala tympani provided a statistically significant enhancement of SGC over untreated deafened ears or deafened ears treated with artificial perilymph. Similar effects were achieved with glial-line-derived neurotrophic factor. BDNF combined with fibroblast growth factor was found to be very effective in stimulating the regrowth of peripheral processes of the SGC into the cochlea. The combination of this treatment with electrical stimulation of the cochlea and continuous injection of growth factors seems to be the most promising intervention for future experiments.

Instead of deafening animals after birth, congenitally deaf animals may serve as a useful model to study the effects of electrical stimulation on the auditory system. Several recent studies have addressed this problem (89, 90, 96, 146, 288), investigating the responses of the auditory system to electrical stimulation in the congenitally deaf white cat. In this strain of animal, the organ of Corti degenerates before the onset of hearing function (24, 179, 374). At birth some of these animals do not have a recognizable organ of Corti; however, even in adult cats 2 yr old, a sufficient number of functionally intact auditory afferents remain, which are suitable for electrical stimulation (96). The process of SGC degeneration proceeds further; therefore, at the age of 6–12 yr, congenitally deaf cats have $<$10% of SGC surviving and display marked structural abnormalities of the synapses of auditory nerve fibers in the cochlear nucleus (288). The absence of click-evoked auditory brain stem responses during the first weeks of life demonstrates that these animals do not have auditory experience. Cortical potentials recorded from the contralateral auditory cortex in response to electrical

stimulation of the cochlea display similar features as those previously recorded in normal hearing animals (89, 90, 255). In addition, the auditory cortex retains some rudimentary level of cochleotopic organization. The process of the disappearance of the cochleotopic organization in the auditory cortex of cats neonatally deafened and investigated 2–5 yr after deafness was confirmed in another study (265), in which the extent of the area with low-threshold electrical activation was larger in deafened animals than in acutely investigated animals. Similarly, in the congenitally deaf white cat, significant deficits in synaptic activity were found in the infragranular cortical layers and a deficit of synaptic activities at longer latencies (149). Klinke et al. (146) were able to recruit almost normal activity in the auditory cortex of these animals by means of an intracochlear implant and accompanying sound processor. The animals were exposed in this way to sounds and conditioned to respond to tones. After months of exposure to normal environmental sound stimuli as well as reinforcement stimuli, which served to dispense of food pellets, the cortical activity in these animals changed. The field potentials became higher in amplitude, expanded in area, developed long latency responses indicative of intracortical information processing, and displayed more synaptic efficacy than in naïve unstimulated animals (Fig. 7). These experiments have shown that valuable animal models are available for the study of cortical plasticity occurring in the process of reestablishing auditory function in deaf children using cochlear implants. Results of several other animal experiments suggest that similarly to the visual system, periods of sensitivity exist in the auditory system in which normal development of the auditory system is disrupted in animals reared under environmental conditions that diminish normally available auditory cues (393). For example, guinea pigs reared from birth in an environment of omnidirectional white noise fail to develop a map of auditory space in the deeper layers of the SC. The critical period of sensitivity lasted only 4 days in this case (between the 26th and 30th day after birth; Ref. 394).

The brain cortical areas may undergo significant remodeling when auditory deprivation supplemented by surgical rewiring occurs at an early developmental age. Already in 1977 (277, 278) it was observed that large visual evoked potentials can be recorded from the primary auditory cortex of cats bilaterally cochleectomized during the first three postnatal weeks. Later Sur et al. (323, 325) reported that neonatal diversion of retinal axons to the auditory thalamus (cross-modal rewiring) in the ferret results in a primary auditory cortex that resem-

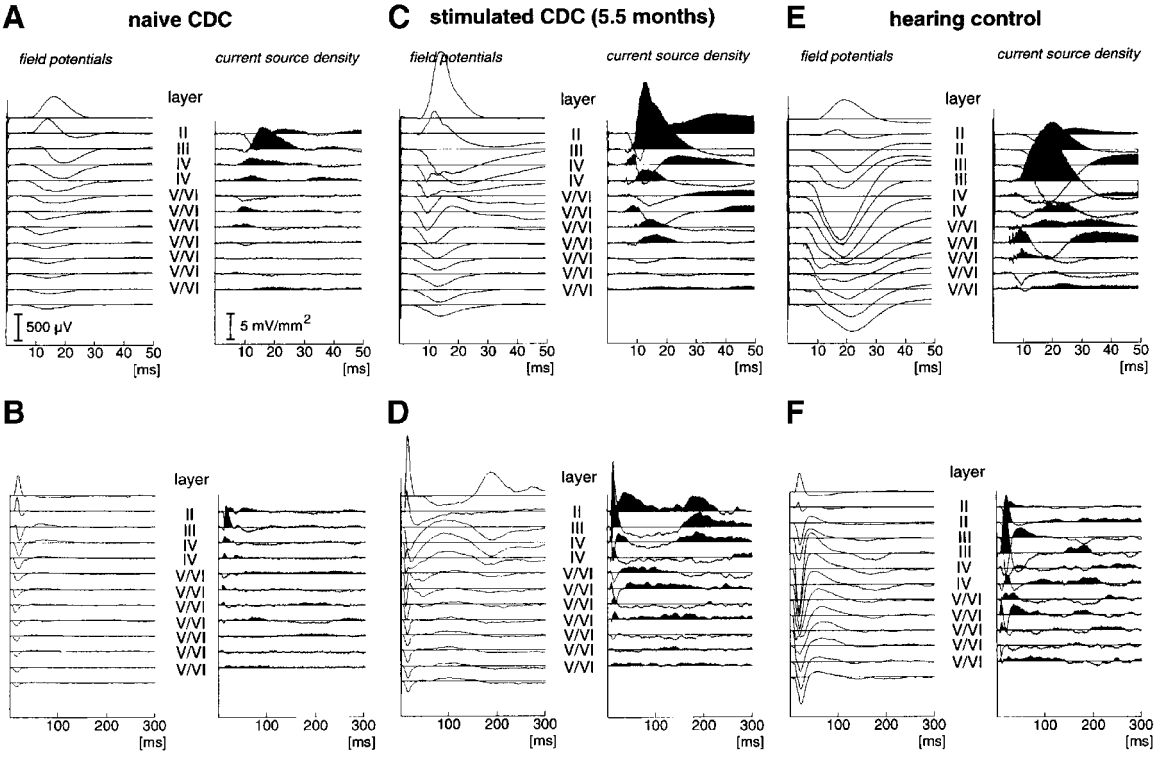

FIG. 7. Current source density analyses in a naïve deaf cat (*A* and *B*), a chronically stimulated deaf cat (*C* and *D*), and an acutely deafened hearing control (*E* and *F*). CDC, congenitally deaf cat. The same data are shown in the *top* and *bottom panels* with different time scales. The topmost recording in field potential is the cortical surface; in current source density, it is at the depth of 300 μm. Further traces with additional 300-μm steps each are shown. Cortical depths are transformed into cortical layers. Shaded areas are sinks. [From Klinke et al. (146), copyright 1999 American Association for the Advancement of Science.]

bles the primary visual cortex in its visual response properties and topography. Projections from the retina to the MGB in neonatal ferrets were induced by ablating the brachium of the IC and the SC and performing lesions of the visual cortex. Later it was shown that the primary auditory cortex of rewired ferrets develops many functional features that are typically characteristic of the visual cortex; cells in the rewired auditory cortex display visual properties such as orientation and direction selectivity, and they encode a two-dimensional map of visual space (283, 284, 304). In behavioral experiments it was demonstrated that when light stimuli are presented to these animals in the portion of the visual field that is "seen" only by this visual projection, they perceive these stimuli to be visual rather than auditory (193). The detailed mechanisms of the functional reorganization of the auditory cortex in rewired animals are not known; however, recent studies suggest that a change in the modality of the afferent input can result in profound changes in cortical circuitry: a reduction in the extent of callosal connections and a reorganization of their pattern (239), and an increase in the extent of horizontal connections and a change in their pattern, so that projections are not restricted to the isofrequency axis (71). The role of patterned activity in the development and plasticity of neuronal circuits is discussed elsewhere (322, 324).

It should be mentioned at this point that significant changes also occur in the visual system when animals are deprived of vision for several years by means of either binocular lid suture shortly after birth or by bilateral enucleation. In the anterior ectosylvian visual area, where in normal cats neurons have purely visual responses, in visually deprived cats most cells reacted to auditory and, to some extent, to somatosensory stimuli (275). Similarly, in visually deprived cats and in bilaterally enucleated cats, the number of auditory-activated neurons increased significantly in the extrastriate visual cortex (suprasylvian areas) and also slightly in the primary visual cortex (400).

B. Changes in the Structure and Function of the Central Auditory System in Humans in Deafness and After Implantation of Auditory Neuroprostheses

The data that have slowly accumulated during the last 10 years give us some hints as how to understand the changes that occur in the central auditory system of humans in either congenital or acquired deafness. For example, studies with magnetoencephalography have shown that in subjects with unilateral idiopathic sudden sensorineural hearing loss, the responses to acoustical stimulation of the healthy ear have shorter latencies and stronger dipole moments over the hemisphere ipsilateral to the stimulation. In some patients one additional source was observed over the anterolateral right hemisphere and another near head midline (354). In those patients who had profound unilateral sensorineural hearing loss from early childhood, the amplitudes and latencies of the evoked responses suggested delayed development (355). Plastic changes in the auditory pathway were also observed in adults with postchildhood onset of profound unilateral deafness (253). Compared with monaurally stimulated normal-hearing subjects, the auditory evoked potentials showed significant increases in interhemispheric waveform, cross-correlation coefficients, and peak amplitude correlations. These increases provide evidence of substantial changes from the normal pattern of asymmetrical (contralateral > ipsilateral amplitude) and asynchronous (contralateral earlier than ipsilateral) central auditory system activation in normal subjects to a much more symmetrical and synchronous activation in the unilaterally deaf.

Several recent studies have demonstrated improved auditory spatial tuning in blind humans (161, 164, 282, 365). Behavioral studies have shown that congenitally blind subjects displayed localization abilities that were superior to those of sighted controls, but only when attending to sounds in peripheral auditory space (282). Early-blind subjects were able to map the three-dimensional auditory environment with equal or better accuracy than sighted subjects. Unlike sighted subjects, they correctly localized sound monaurally (164). Electrophysiological recordings obtained at the same time revealed sharper tuning of early spatial attention mechanisms in the blind subjects (282). With the aid of positron emission tomography, the activation of cortical areas was compared in a localization task between sighted and congenitally blind subjects (365); both groups strongly activated posterior parietal areas, but only the blind subjects activated association areas in the right occipital cortex, the foci of which were similar to areas previously identified in visual location and motion detection experiments in sighted subjects. This finding corresponds with the results of recordings of auditory evoked potentials in blind subjects, who displayed robust N1 and P3 components of these potentials also over the occipital cortical region (161).

More than 20 years of experience with cochlear implants (CI) allow us to evaluate the changes that occur in patients using implants for several years. It is a common experience that all subjects wearing cochlear implants show continuous improvement in their ability to hear several years after implantation (69, 351–353). Studies examining the performance of CI recipients over time have indicated that most gains in performance with CI occur in the first 9–12 mo of use. This holds true particularly for postlingually deaf adults, although some patients show continued improvement during 4 or 5 years of implant use. Adults who have been deaf for many years

and who received their implant when they were older tend not to perform as well as adults who have been deaf for only a few years or who received their implant when they were younger. In children the benefit of implants depends mostly on whether the implants were received pre- or postlingually. The results are better in postlingually implanted children than in prelingually implanted children. Compared with postlingually deafened children or adults, prelingually deaf children require more time to learn to use their implants. In prelingually deaf children, the age when they received implants was also critical. This finding points to a critical period of brain plasticity for acquiring language in children. Although there was no significant difference in closed-set tests of speech perception ability between children implanted before age 5 compared with children implanted after age 5, open-set word recognition performance was significantly better for children implanted before age 5 at the 48-mo interval (69).

Few studies with objective measurements of changes in the brain of subjects with cochlear implants are available at the present time. The first PET imaging studies demonstrated a revival of brain metabolic activity in auditory cortex areas of deaf people after implantation (103, 114, 115, 226). The comparison of brain activation in normal-hearing and CI subjects listening to speech and nonspeech revealed some differences in the activation of the brain hemispheres (395). While implanted subjects activated by sentence tests had more foci in the right temporal regions, where lateralized mechanisms for prosodic (pitch) processing are well established, normal-hearing subjects showed a focus in the left inferior frontal gyrus, where semantic processing has been implicated. Differences were also found between both groups in tests investigating activation in a "cocktail party" situation, i.e., differentiation of several voices speaking at once. In another recent study (227) cerebral blood flow in postlingually deafened CI users was compared with that in normal hearing subjects using PET. While noise activation in CI users did not significantly differ from that in normal subjects, hearing speech activated more cortical areas in CI users than in normal subjects. A comparison of speech activation in these two groups revealed higher activation in CI users not only in the temporal cortices but also in Broca's areas and its right hemisphere homolog, the supplementary motor area, and the anterior cingulated gyrus. Activation of the auditory cortex with the simultaneous presentation of auditory and visual (sign language) input was found in long-term users of the cochlear implants in a PET study, whereas the auditory cortex was not activated in short-term users (231). This corresponds with the fact that the sign language was found to activate the auditory cortex in a PET study in congenitally deaf subjects (232). Similar activation in the classical language areas of the left hemisphere was observed with fMRI in deaf subjects when processing their native language, which was either English or American Sign Language (229). Activation was found in native signers also in homologous areas in the right hemisphere.

Several studies on auditory system plasticity in children wearing CI concentrated on investigating cortical evoked potentials (60, 250, 251). The latency of the first positive (P_1) component of the late cortical potential was used as an indicator of auditory system maturation. For normal hearing children there is a gradual evolution of evoked potential features that extends throughout adolescence with P_1 latency becoming adultlike at about age 15. The time to maturity in implanted subjects is delayed by an amount approximately equal to the duration of deafness. Thus the 5-yr delay for maturation of P_1 latency roughly corresponded to the average 4.5-yr interval between the onset of deafness and the time of implantation (251). Similar authors (252) recently observed that compared with cortical auditory evoked potentials mismatch negativity, i.e., a cortical potential elicited by an irregularity in otherwise regular repetition of acoustical stimuli, is a better measure of basic auditory processes necessary for the development of spoken-language perception skills in profoundly deaf children and adults wearing cochlear implants.

VII. CONCLUSIONS

The auditory system, like other sensory systems, is plastic, and as such is able to reorganize its structure and function after partial or total loss of receptor function. Unlike the visual system receptors, the receptors of the auditory system are very vulnerable, and an overstimulation by intense sound may significantly alter their function, leading first to temporary threshold shifts and, in the case of prolonged or very intensive exposure, to permanent threshold shifts. Ultimately, the receptors die out, triggering a sequence of changes in the whole auditory system starting with the spiral ganglion cells and ending in the auditory cortex. Regardless of whether the loss of receptors (hearing loss) is based on mechanical lesions, ablations, chemical lesions by ototoxic drugs, noise-induced damage of hair cells, or programmed loss connected with aging, the sequence of basic changes in the central auditory system is similar and results in the reorganization of the cortical projection areas and, in some cases, the subcortical areas such as the IC.

Structural changes are visible in some parts of the auditory system depending on whether the hearing loss occurred during the early developmental period or in adults. In developing animals the structural changes comprise a reduction in the number of neurons in the nuclei of the auditory pathway and the formation of new connections, which would not occur in normal intact animals. In the case of unilateral ablations, the reorganization of the

auditory pathway serves to strengthen the functional role of the intact ear. Independent of whether unilateral ablation occurs in a developing or adult animal, the pathway from the intact ear to the ipsilateral cortex is strengthened, assuming tasks that in normal animals are typically associated with the contralateral auditory cortex. In adult animals, hearing loss is accompanied by the activation of proteins such as calbindin, parvalbumin, or GAP-43, which are normally present in the auditory system during development. After hearing loss in adult animals, significant changes also occur in the inhibitory mediators in the auditory pathway. The results of many electrophysiological investigations suggest that inhibition in the auditory system is significantly downregulated after hearing loss. The downregulation of inhibitory processes also accompanies aging and occurs as a result of noise exposure. It remains to be investigated to what extent hearing loss triggers the activation of neurotrophins in the central auditory system such as nerve growth factor, BDNF, neurotrophins, and others. Nerve growth factors have been shown to be involved in the plasticity of both developing and adult visual cortex (for review, see Refs. 344, 345) and can prevent the loss of SGC after deafening with ototoxic drugs as well as support postnatal SGC in culture (for review, see Ref. 183). Partial hearing loss in experimental animals results in the reorganization of cortical topographical maps with an enlarged representation of those frequency ranges corresponding to the borders of the cochlear lesions. A similar situation occurs after damage to the visual and somatosenory systems (274). The mechanisms of the reorganization are so far unknown and remain to be elucidated. The major mechanisms that have been postulated to account for injury-induced reorganization include *1*) immediate unmasking of normally unexpressed inputs as a consequence of the removal of inhibition; *2*) strengthening of previously ineffective or weakly effective synaptic inputs, perhaps as a consequence of some form of Hebbian mechanism; and *3*) axonal proliferation (and possible synaptogenesis) within the axonal arbors of long-range intracortical horizontal projection fibers or of thalamocortical fibers (113).

The mechanisms of cortical as well as subcortical plasticity in the auditory system are, similarly as in other sensory systems, frequently considered to be directed by Hebbian rules (95). Broadly interpreted, according to these rules correlated pre- and postsynaptic activity would increase synaptic strength, and uncorrelated activity would decrease synaptic strength. For example, retuning the receptive fields in the auditory cortex during classical conditioning is hypothesized to depend on changes in cortical synapses if the UC produces widespread postsynaptic excitation by the release of acetylcholine (366, 367). Cholinergic involvement in cortical plasticity is supported by the finding of cortical map reorganization induced by the pairing of acoustical stimuli with electrical stimulation of the nucleus basalis (138). The input from the basal forebrain is mainly carried out by neurons that use acetylcholine as a neurotransmitter. After unilateral lesion of the basal forebrain, expansion of the adjacent regions into the somatosensory cortex region representing the injured part of skin does not occur (127). There are many other experimental proofs to support the hypothesis that acetylcholine is involved in plasticity in the central auditory system. In addition to the important role of acetylcholine in auditory cortical plasticity, it cannot be excluded that glutamate-induced plasticity is also involved. Long-term potentiation and long-term depression are postulated to be the cellular correlates of plasticity in the visual cortex. In this model, NMDA receptors act as detectors of correlated neural activity (for review, see Ref. 274). The blockade of NMDA receptors prevents the plasticity commonly associated with monocular lid suture.

Another transmitter, which certainly plays an important role in auditory plasticity, is GABA. The lack of this inhibitory neurotransmitter is considered to be a reason for the physiologically defined unmasking of normally silent inputs in deprived sensory cortex (29, 72, 116). The normal spread of the afferent terminals is larger than what is reflected in the physiologically determined excitatory receptive fields. The expression of latent inputs is inhibited at least partially by GABA or glycinergic interneurons. According to these theories, removal of the normal cortical surround inhibition (i.e., inhibition surrounding excitatory receptive fields) would unmask latent or suppressed inputs to the cortical areas deprived of their normal representations by peripheral damage. Receptor damage in the cochlea results in the loss of surround inhibition in cortical neurons; however, it does not produce a reorganization of the topographic map of the cochlea in the auditory cortex (266). The decrease in the level of cortical inhibitory neurotransmitters may be a reason for the temporarily enhanced cortical evoked responses observed in experimental animals after noise exposure (257, 334).

In addition to the physiological changes in neurotransmitters, auditory plasticity might also involve anatomic changes, such as the growth of new horizontal connections, the expansion of axonal arbors, or structural alterations of synapses. Such changes are known from other sensory systems in different animal models (43, 44, 66, 75). Neurotrophins and growth factors undoubtedly play an important role in the anatomic changes connected with plasticity. Their potential role in the plasticity of the auditory system remains to be elucidated.

The unique information provided by the results of experiments with electrical stimulation of the auditory nerve fibers, and particularly the results of hearing rehabilitation with cochlear implants, contributes to our understanding of brain plasticity. These results support the view that the auditory system is flexible and possesses a

potential for dynamic changes as demonstrated in experiments with auditory conditioning. An understanding of the plasticity of the auditory system is especially important with respect to speech sound perception and speech discrimination learning (151–153). Understanding impairments of acoustical signal processing, particularly during the period of language learning, enables the development of methods for the remediation of such impairments and is of great practical help for children with language-based learning impairments, including dyslexia and autism (194, 338). Moreover, practical knowledge of the mechanisms of auditory system plasticity may stimulate new developments in the rehabilitation of hearing function with hearing aids and cochlear implants and contribute to alleviating the consequences of hearing loss induced by aging and noise exposure.

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REFERENCES

1. Abbott SD, Hughes LF, Bauer CA, Salvi R, and Caspary DM. Detection of glutamate decarboxylase isoforms in rat inferior colliculus following acoustic exposure. *Neuroscience* 93: 1375–1381, 1999.
2. Adams JC and Schulte BA. Histopathologic observations of the aging gerbil cochlea. *Hear Res* 104: 101–111, 1997.
3. Ahissar M, Protopapas A, Reid M, and Merzenich MM. Auditory processing parallels reading abilities in adults. *Proc Natl Acad Sci USA* 97: 6832–6837, 2000.
4. Ahissar E, Vaadia E, Ahissar M, Bergman H, Aarieli A, and Abeles M. Dependence of cortical plasticity on correlated activity of single neurons and on behavioral context. *Science* 257: 1412–1415, 1992.
5. Altschuler RA, Cho Y, Ylikoski J, Pirvola U, Magal E, and Miller JM. Rescue and regrowth of sensory nerves following differentiation by neurotrophic factors. *Ann NY Acad Sci* 884: 305–311, 1999.
6. Altschuler RA, Lim HH, Ditto J, Dolan D, and Raphael Y. Protective mechanisms in the cochlea: heat shock proteins. In: *Auditory System Plasticity and Regeneration*, edited by Salvi RJ and Henderson D. New York: Thieme Medical, 1996, p. 202–212.
7. Anniko M, Sjostrom B, and Webster D. The effects of auditory deprivation on morphological maturation of the ventral cochlear nucleus. *Arch Oto-Laryngol* 246: 43–47, 1989.
8. Araki Kawano SA, Seldon HL, Shepherd RK, Funasaka S, and Clark GM. Effects of chronic electrical stimulation on spiral ganglion neuron survival and size in deafened kittens. *Laryngoscope* 108: 687–695, 1998.
9. Arehole S, Salvi RJ, Saunders SS, and Henderson D. Evoked response "forward masking" patterns in chinchillas with temporary hearing loss. *Hear Res* 27: 193–205, 1987.
10. Ashe JH, McKenna TM, and Weinberger NM. Cholinergic modulation of frequency receptive fields in auditory cortex. II. Frequency effects of anticholinesterases provide evidence for a modularly action of androgenous ACh. *Synapse* 4: 44–54, 1989.
11. Axelsson A, Borchgrevink HM, Hamernik RP, Hellström PA, Henderson D, and Salvi RJ. (Editors). *Scientific Basis of Noise-Induced Hearing Loss*. New York: Thieme, 1996.
12. Bakin JS, Lepan B, and Weinberger NM. Sensitization induced receptive field plasticity in the auditory cortex is independent of CS-modality. *Brain Res* 577: 226–235, 1992.
13. Bakin JS, South DA, and Weinberger NM. Induction of receptive field plasticity in the auditory cortex of the guinea pig during instrumental avoidance conditioning. *Behav Neurosci* 110: 905–913, 1996.
14. Bakin JS and Weinberger NM. Classical conditioning induces CS-specific receptive field plasticity in the auditory cortex of the guinea pig. *Brain Res* 536: 271–286, 1990.
15. Bakin JS and Weinberger NM. Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proc Natl Acad Sci USA* 93: 11219–11224, 1996.
16. Bjordahl TS, Dimyan MA, and Weinberger NM. Induction of long-term receptive field plasticity in the auditory cortex of the waking guinea pig by stimulation of the nucleus basalis. *Behav Neurosci* 112: 467–479, 1998.
17. Bledsoe SC Jr, Agase SN, Altschuler RA, and Miller JM. Changes in the central auditory system with deafness and return of activity via a cochlear prosthesis. In: *Acoustical Signal Processing in the Central Auditory System*, edited by Syka J. New York: Plenum, 1997, p. 513–528.
18. Bledsoe SC Jr, Agase SN, Miller JM, and Altschuler RA. Deafness-induced plasticity in the mature central auditory system. *Neuroreport* 7: 225–229, 1995.
19. Bock GR and Saunders JC. Effects of low and high frequency noise bands in producing a physiologic correlate of loudness recruitment in mice. *Trans Am Acad Ophthal Otol* 82: 338–342, 1976.
20. Boettcher FA, Mills JH, Dubno JR, and Schmidt RA. Masking of auditory brainstem response in young and aged Mongolian gerbils. *Hear Res* 89: 1–13, 1995.
21. Boettcher FA, Mills JH, and Norton LB. Age-related changes in auditory evoked potentials of gerbils. I. Response amplitudes. *Hear Res* 71: 137–145, 1993.
22. Boettcher FA and Salvi RJ. Functional changes in the ventral cochlear nucleus following acute acoustic overstimulation. *J Acoust Soc Am* 94: 2123–2134, 1993.
23. Bohne BA, Gruner MM, and Harding GW. Morphological correlates of aging in the chinchilla cochlea. *Hear Res* 48: 79–92, 1990.
24. Bosher SK and Hallpike CS. Observations on the histological features, development, and pathogenesis of the inner ear degeneration of the deaf white cat. *Proc R Soc Lond* 162: 147–170, 1965.
25. Buchwald JS, Halas ES, and Schramm S. Changes in cortical and subcortical unit activity during behavioral conditioning. *Physiol Behav* 1: 11–22, 1966.
26. Buzsaki G and Gage FH. The cholinergic nucleus basalis: a key structure in neocortical arousal. In: *Central Cholinergic Synaptic Transmission*, edited by Frotscher M and Misgeld U. Basel: Birkhauser Verlag, 1989, p. 159–171.
27. Caicedo A, D'Aldin CH, Eybalin M, and Puel JL. Temporary sensory deprivation changes calcium-binding proteins levels in the auditory brainstem. *J Comp Neurol* 378: 1–15, 1997.
28. Calford MB, Rajan R, and Irvine DRF. Rapid changes in the frequency tuning of neurons in cat auditory cortex resulting from pure-tone induced temporary threshold shift. *Neuroscience* 55: 953–964, 1993.
29. Calford MB and Tweedale T. Immediate and chronic changes in responses of somatosensory cortex in adult flying-fox after digit amputation. *Nature* 332: 446–448, 1988.
30. Canlon B. The effects of sound conditioning on the cochlea. In: *Auditory System Plasticity and Regeneration*, edited by Salvi RJ, Henderson D, Fiorino F, and Colletti V. New York: Thieme Medical, 1996, p. 118–127.
31. Canlon B, Borg E, and Flock A. Protection against noise trauma by pre-exposure to a low level acoustic stimulus. *Hear Res* 34: 197–200, 1988.
32. Caspary DM, Holder TM, Hughes LF, Milbrandt JC, McKernan RM, and Naritoku DK. Age-related changes in GABA(A) receptor subunit composition and function in rat auditory system. *Neuroscience* 93: 307–312, 1999.
33. Caspary DM, Milbrandt JC, and Helfert RH. Central auditory aging: GABA changes in the inferior colliculus. *Exp Gerontol* 30: 349–360, 1995.
34. Caspary DM, Raza A, Lawhorn Armour BA, Pippin J, and Arneric SP. Immunocytochemical and neurochemical evidence for age-related

loss of GABA in the inferior colliculus: implications for neural presbycusis. *J Neurosci* 10: 2363–2372, 1990.
35. CLAREY JC, TWEEDALE R, AND CALFORD MB. Interhemispheric modulation of somatosensory receptive fields: evidence for plasticity in primary somatosensory cortex. *Cereb Cortex* 6: 196–206, 1996.
36. CODY AR AND JOHNSTONE BM. Temporary threshold shift modified by binaural acoustic stimulation. *Hear Res* 6: 199–206, 1982.
37. COLEMAN J. Effects of acoustic deprivation on morphological parameters of development of auditory neurons in rat. In: *Neuronal Mechanisms of Hearing*, edited by Syka J and Aitkin L. New York: Plenum, 1981, p. 359–362.
38. COLEMAN J, BLATCHLEY BJ, AND WILLIAMS JE. Development of the dorsal and ventral cochlear nuclei in rat and effects of acoustic deprivation. *Dev Brain Res* 4: 119–123, 1982.
39. COVELL WP AND ROGERS JB. Pathological changes in the inner ears of senile guinea pigs. *Laryngoscope* 67: 118–129, 1957.
40. CRANFORD JL, BOOSE M, AND MOORE CA. Effects of aging on the precedence effect in sound localization. *J Speech Hear Res* 33: 654–659, 1990.
41. CRUIKSHANK SJ AND WEINBERGER NM. Receptive-field plasticity in the adult auditory cortex induced by Hebbian covariance. *J Neurosci* 16: 861–875, 1996.
42. DANCER AL, HENDERSON D, SALVI RJ, AND HAMERNIK RP. (Editors). *Noise-Induced Hearing Loss*. St. Louis, MO: Mosby Yearbook, 1992.
43. DARIAN-SMITH C AND GILBERT CD. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. *Nature* 368: 737–740, 1994.
44. DARIAN-SMITH C AND GILBERT CD. Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated. *J Neurosci* 15: 1631–1647, 1995.
45. DAYAL VS AND BHATTACHARYYA TK. Comparative study of age-related cochlear hair cell loss. *Ann Otol Rhinol Laryngol* 95: 510–513, 1986.
46. DEUTSCH JA. The cholinergic synapse and the site of memory. *Science* 174: 788–794, 1971.
47. DIAMOND DM AND WEINBERGER NM. Classical conditioning rapidly induces specific changes in frequency receptive fields of single neurons in secondary and ventral ectosylvian auditory cortical fields. *Brain Res* 372: 357–360, 1986.
48. DINSE HR, RECANZONE GH, AND MERZENICH MM. Alterations in correlated activity parallel ICMS-induced representational plasticity. *Neuroreport* 5: 173–176, 1993.
49. DISTERHOFT JF AND OLDS J. Differential development of conditioned unit changes in thalamus and cortex of rat. *J Neurophysiol* 35: 665–679, 1972.
50. DUM N. Age-dependence of the auditory threshold-difference between albino and pigmented guinea pigs *(Cavia porcellus)*. *Zeitschrift Saugetierkunde* 48: 95–99, 1983.
51. DUM N AND VON WEDEL H. Langzeituntersuchung alterbedingter Veranderungen der Hirnstammpotentiale beim Meerschweinchen. *Laryngol Rhinol Otol* 62: 378–381, 1983.
52. EDELINE JM. Does Hebbian synaptic plasticity explain learning-induced sensory plasticity in adult mammals? *J Physiol (Lond)* 90: 271–276, 1996.
53. EDELINE JM, HARS B, AND HENNEVIN E. Transient and prolonged facilitation of tone-evoked responses induced by basal forebrain stimulations in the rat auditory cortex. *Exp Brain Res* 97: 373–386, 1994.
54. EDELINE JM, MAHO C, HARS B, AND HENNEVIN E. Non-awaking basal forebrain stimulation enhances auditory cortex responsiveness during slow-wave sleep. *Brain Res* 636: 333–337, 1994.
55. EDELINE JM, PHAM P, AND WEINBERGER NM. Rapid development of learning-induced receptive field plasticity in the auditory cortex. *Behav Neurosci*.107: 539–557, 1993.
56. EDELINE JM AND WEINBERGER NM. Subcortical adaptive filtering in the auditory system: associative receptive field plasticity in the dorsal medial geniculate body. *Behav Neurosci* 105: 154–175, 1991.
57. EDELINE JM AND WEINBERGER NM. Thalamic short-term plasticity in the auditory system: associative returning of receptive fields in the ventral medial geniculate body. *Behav Neurosci* 105: 618–639, 1991.
58. EDELINE JM AND WEINBERGER NM. Associative retuning in the thalamic source of inpult to the amygdala and auditory cortex: receptive field plasticity in the medial division of the medial geniculate body. *Behav Neurosci* 106: 81–105, 1992.
59. EDELINE JM AND WEINBERGER NM. Receptive field plasticity in the auditory cortex during frequency discrimination training: selective returning independent of task difficulty. *Behav Neurosci* 107: 82–103, 1993.
60. EGGERMONT JJ, PONTON CW, DON M, WARING MD, AND KWONG B. Maturational delays in cortical evoked potentials in cochlear implant users. *Acta Otolaryngol* 117: 161–163, 1997.
61. ELBERT T, PANTEV C, WIENBRUCH C, ROCKSTROH B, AND TAUB E. Increased cortical representation of the fingers of the left hand in string players. *Science* 270, 305–307, 1996.
62. EVANS EF AND BORERWE TA. Ototoxic effects of salicylates on the responses of single cochlear nerve fibres and on cochlear potentials. *Br J Audiol* 16: 101–108, 1982.
63. FIEZ J, TALLAL P, RAICHLE M, MIEZIN F, KATZ W, AND PETERSON S. PET studies of auditory and phonological processing: effects of stimulus characteristics and task demands. *J Cogn Neurosci* 7: 357–375, 1995.
64. FINLAYSON PG AND CASPARY DM. Response properties in young and old Fischer-344 rat lateral superior olive neurons: a quantitative approach. *Neurobiol Aging* 14: 127–139, 1993.
65. FITZGIBBONS PJ AND GORDON-SALANT S. The intelligibility of sentences in quiet and in noise in aged listeners. *J Acoust Soc Am* 74: 1136–1144, 1983.
66. FLORENCE SL, TAUB HB, AND KAAS JH. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science* 282: 1117–1121, 1998.
67. FORSTER CR AND ILLING RB. Plasticity of the auditory brainstem: cochleotomy-induced changes of Calbindin-D28k expression in the rat. *J Comp Neurol* 416: 173–187, 2000.
68. FRIDBERGER A, FLOCK A, ULFENDAHL M, AND FLOCK B. Acoustic overstimulation increases outer hair cell Ca^{2+} concentrations and causes dynamic concentrations of the hearing organ. *Proc Natl Acad Sci USA* 95: 7127–7132, 1998.
69. FRYAUF-BERTSCHY H, TYLER RS, KELSAY DMR, GANTY BJ, AND WOODWORTH GG. Cochlear implant use by prelingually deafened children: the influences of age at implant and length of device use. *J Speech Language Hear Res* 40: 183–199, 1997.
70. GAO E AND SUGA N. Experience-dependent plasticity in the auditory cortex and the inferior colliculus of bats: role of the corticofugal system. *Proc Natl Acad Sci USA* 97: 8081–8086, 2000.
71. GAO WJ AND PALLAS SL. Cross-modal reorganization of horizontal connectivity in auditory cortex without altering thalamocortical projections. *J Neurosci* 19: 7940–7950, 1999.
72. GARRAGHTY PE, LACHICA EA, AND KAAS JH. Injury-induced reorganization of somatosensory cortex is accompanied by reductions in GABA staining. *Somatosens Motor Res* 8: 347–354, 1991.
73. GATEHOUSE S. Apparent auditory deprivation effects of late onset: the role of presentation level. *J Acoust Soc Am* 86: 2103–2106, 1989.
74. GATEHOUSE S. The time course and magnitude of perceptual acclimatization to frequency responses: evidence from monaural fitting of hearing aids. *J Acoust Soc Am* 92: 1258–1268, 1992.
75. GILBERT CD. Adult cortical dynamics. *Physiol Rev* 78: 467–485, 1998.
76. GIRAUD AL, CHERY-CROZE S, FISCHER G, VIGHETTO A, GREGOIRE MC, LAVENNE F, AND COLLET L. A selective imaging of tinnitus. *Neuroreport* 10: 1–5, 1999.
77. GIRAUDI-PERRY DM, SALVI RJ, AND HENDERSON D. Gap detection in hearing-impaired chinchillas. *J Acoust Soc Am* 72: 1387–1393, 1982.
78. GLASBERG BR, MOORE CJ, AND BACON SP. Gap detection and masking in hearing-impaired and normal-hearing subjects. *J Acoust Soc Am* 81: 1546–1556, 1987.
79. GONZALES-LIMA F AND SCHEICH H. Neural substrates for tone-conditioned bradycardia demonstrated with 2-deoxyglucose. I. Activation of auditory nuclei. *Behav Brain Res* 14: 213–233, 1984.
80. GONZALES-LIMA F AND SCHEICH H. Neural substrates for tone-conditioned bradycardia demonstrated with 2-deoxyglucose. II. Auditory cortex plasticity. *Behav Brain Res* 20: 281–293, 1986.
81. GRATTON MA, SCHMIEDT RA, AND SCHULTE BA. Age-related decreases in endocochlear potential are associated with vascular abnormalities in the stria vascularis. *Hear Res* 102: 181–190, 1996.

82. HALL RD. Estimation of surviving spiral ganglion cells in the deaf rat using the electrically evoked auditory brainstem response. *Hear Res* 49: 155–168, 1990.
83. HARDIE NA, MARTSI-MCCLINTOCK A, AITKIN LM, AND SHEPHERD RK. Neonatal sensorineural hearing loss affects synaptic density in the auditory midbrain. *Neuroreport* 9: 2019–2022, 1998.
84. HARDIE NA AND SHEPHERD RK. Sensorineural hearing loss during development: morphological and physiological response of the cochlea and auditory brainstem. *Hear Res* 128: 147–165, 1999.
85. HARRISON J AND BUCHWALD J. Auditory brainstem responses in the aged cat. *Neurobiol Aging* 3: 163–171, 1982.
86. HARRISON RV, IBRAHIM D, STANTON SG, AND MOUNT RJ. Reorganization of frequency maps in chinchilla auditory midbrain after long-term basal cochlear lesions induced at birth. In: *Auditory System Plasticity and Regeneration*, edited by Salvi RJ, Henderson D, Fiorino F, and Colletti V. New York: Thieme Medical, 1996, p. 238–255.
87. HARRISON RV, NAGASAWA A, SMITH DW, STANTON S, AND MOUNT RJ. Reorganization of auditory cortex after neonatal high frequency cochlear hearing loss. *Hear Res* 54: 11–19, 1991.
88. HARTGRAVES SL, MENSAH PL, AND KELLY PH. Regional decreases of cortical choline acetyltransferase after lesions of the septal area and in the area of nucleus basalis magnocellularis. *Neuroscience* 7: 2369–2376, 1982.
89. HARTMANN R, KLINKE R, AND HEID S. Functional organization of the auditory cortex in the congenitally deaf white cat. In: *Acoustical Signal Processing in the Central Auditory System*, edited by Syka J. New York: Plenum, 1997, p. 561–576.
90. HARTMANN R, SHEPHERD RK, HEID S, AND KLINKE R. Response of the primary auditory cortex to electrical stimulation of the auditory nerve in the congenitally deaf white cat. *Hear Res* 112: 115–133, 1997.
91. HARTSHORN DO, MILLER JM, AND ALTSCHULER RA. Protective effect of electrical stimulation in the deafened guinea pig cochlea. *Otolaryngol Head Neck Surg* 104: 311–319, 1991.
92. HASHISAKI GT AND RUBEL EW. Effects of unilateral cochlea removal on anteroventral cochlear nucleus neurons in developing gerbils. *J Comp Neurol* 283: 465–473, 1989.
93. HAWKINS JE, MILLER JM, ROUSE RC, DAVIS JA, AND RAREY K. Inner ear histopathology in aging rhesus monkeys (*Macaca mulatta*). In: *Behavior and Pathology of Aging Rhesus Monkeys.* New York: Liss, 1985, p. 137–154.
94. HAZELL JWP, MEERTON LJ, AND CONWAY JJ. Electrical tinnitus suppression (ETS) with a single channel cochlear implant. *J Laryngol Otol Suppl* 18: 39–44, 1989.
95. HEBB DO. *The Organization of Behavior*. New York: Wiley, 1949.
96. HEID S, HARTMANN R, AND KLINKE R. A model for prelingual deafness, the congenitally deaf white cat: population statistics and degenerative changes. *Hear Res* 115: 101–112, 1998.
97. HELLSTROM LI AND SCHMIEDT RA. Compound action potential input/output functions in young and quiet-aged gerbils. *Hear Res* 50: 163–174, 1990.
98. HENDERSON D AND SALVI RJ. Effects of noise exposure on the auditory functions. *Scand Audiol* 27: 63–73, 1998.
99. HENDRY SHC AND JONES EG. Reduction in number of immunostained GABAergic neurones in deprived-eye dominance columns of monkey area 17. *Nature* 320: 750–753, 1986.
100. HENRY KR. Age-related changes in sensitivity of the postpubertal ear to acoustic trauma. *Hear Res* 8: 285–294, 1982.
101. HENRY KR. Aging and audition. In: *Auditory Psychobiology of the Mouse*, edited by Willott JF. Springfield, IL: Thomas, 1983, p. 470–493.
102. HENRY KR AND CHOLE RA. Genotypic differences in behavioral, physiological, and anatomical expressions of age-related hearing loss on the laboratory mouse. *Audiology* 19: 369–383, 1980.
103. HERZOG H, LAMPRECHT A, KUHN A, RODEN W, VOSTEEN KH, AND FINENDEGEN LE. Cortical activation in profoundly deaf patients during cochlear implant stimulation demonstrated by $H_2{}^{15}O$ PET. *J Comput Assist Tomogr* 15: 369–375, 1991.
104. HOKE ES, HOKE M, AND ROSS B. Neurophysiological correlate of the auditory after-image ("Zwicker tone"). *Audiol Neurootol* 1: 161–174, 1996.
105. HOKE ES, MÜHLNICKEL W, ROSS B, AND HOKE M. Tinnitus and event-related activity of the auditory cortex. *Audiol Neurootol* 3: 300–331, 1998.
106. HORVÁTH M, FORSTER CR, AND ILLING BR. Postnatal development of GAP-43 immunoreactivity in the auditory brainstem of the rat. *J Comp Neurol* 382: 104–115, 1997.
107. HOUSE JW AND BRACKMAN DE. Tinnitus: surgical treatment. In: *CIBA Foundation Symposium 85: Tinnitus*, edited by Evered D and Lawrenson G. London: Pitman, 1981, p. 204–212.
108. HUBEL DH. Exploration of the primary visual cortex. *Nature* 299: 515–524, 1982.
109. HUNTER KP AND WILLOTT JF. Aging and the auditory brainstem response in mice with severe or minimal presbycusis. *Hear Res* 30: 207–218, 1987.
110. ILLING RB, HORVÁTH M, AND LASZIG R. Plasticity of the auditory brainstem: effects of cochlear ablation on GAP-43 immunoreactivity in the rat. *J Comp Neurol* 382: 116–138, 1997.
111. INGHAM NJ, COMIS SD, AND WITHINGTON DJ. Hair cell loss in the aged guinea pig cochlea. *Acta Otolaryngol* 119: 42–47, 1999.
112. INGHAM NJ, THORNTON SK, COMIS SP, AND WITHINGTON DJ. The auditory brainstem response of aged guinea pigs. *Acta Otolaryngol* 118: 673–680, 1998.
113. IRVINE DRF AND RAJAN R. Injury- and use-related plasticity in the primary sensory cortex of adult mammals: possible relationship to perceptual learning. *Clin Exp Pharm Physiol* 23: 939–947, 1996.
114. ITO J, IWASAKI Y, SAKAKIBARA J, AND YONEKURA Y. Positron emission tomography of auditory sensation in deaf patients and patients with cochlear implants. *Ann Otol Rhinol Laryngol* 102: 797–801, 1993.
115. ITO J, SAKAKIBARA J, HONJO I, IWASAKI Y, AND YONEKURA Y. Positron emission tomographic study of auditory sensation in a patient with a cochlear implant. *Arch Otolaryngol Head Neck Surg* 116: 1437–1439, 1990.
116. JACOBS KM AND DONOGHUE JP. Reshaping the cortical motor map by unmasking latent intracortical connections. *Science* 251: 944–947, 1991.
117. JACONO AA, HU B, KOPKE RD, HENDERSON D, VAN DER WATER TR, AND STEINMAN HM. Changes in cochlear antioxidant enzyme activity after sound conditioning and noise exposure in the chinchilla. *Hear Res* 117: 31–38, 1998.
118. JAIN N, FLORENCE SL, AND KAAS JH. Reorganization of somatosensory cortex after nerve and spinal cord injury. *News Physiol Sci* 13: 143–149, 1998.
119. JASTREBOFF PJ AND HAZELL JWP. A neurophysiological approach to tinnitus: clinical implications. *Br J Audiol* 27: 7–17, 1993.
120. JASTREBOFF PJ AND SASAKI CT. Salicylate-induced changes in spontaneous activity of single units in the inferior colliculus of the guinea pig. *J Acoust Soc Am* 80: 1384–1391, 1986.
121. JEAN-BAPTISTE M AND MOREST DK. Transneuronal changes of synaptic endings and nuclear chromatin in the trapezoid body following cochlear ablations in cats. *J Comp Neurol.*162: 111–135, 1975.
122. JERGER JF. Influence of stimulus duration on the pure-tone threshold during recovery from auditory fatigue. *J Acoust Soc Am* 27: 121–124, 1955.
123. JI W, GAO E, AND SUGA N. Effects of acetylcholine and atropine on plasticity of central auditory neurons caused by conditioning in bats. *J Neurophysiol* 86: 211–215, 2001.
124. JOHNSTON MV, MCKINNEY M, AND COYLE JT. Evidence for a cholinergic projection to neocortex from neurons in the basal forebrain. *Proc Natl Acad Sci USA* 76: 5392–5396, 1979.
125. JOHNSTON MV, MCKINNEY M, AND COYLE JT. Neocortical cholinergic innervations: a description of extrinsic and intrinsic components in the rat. *Exp Brain Res* 43: 159–172, 1981.
126. JOHNSTONE BM, PATUZZI R, SYKA J, AND SYKOVÁ E. Stimulus-related potassium changes in the organ of Corti of guinea-pig. *J Physiol (Lond)* 408: 77–92, 1989.
127. JULIANO SL, MA W, AND ESLIN D. Cholinergic depletion prevents expansion of topographic maps in somatosensory cortex. *Proc Natl Acad Sci USA* 88: 780–784, 1991.
128. JYUNG RW, MILLER JM, AND CANNON SC. Evaluation of eighth nerve integrity by the electrically evoked middle latency response. *Arch Otolar-Head Neck Surgery* 101: 670–682, 1989.
129. KAAS JH. Plasticity of sensory and motor maps in adult mammals. *Annu Rev Neurosci* 14: 137–167, 1991.
130. KAAS JH, MERZENICH MM, AND KILLACKEY HP. The reorganization of

somatosensory cortex following peripheral nerve damage in adult and developing mammals. *Annu Rev Neurosci* 6: 325–356, 1983.
131. KALTENBACH JA AND AFMAN CE. Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. *Hear Res* 140: 165–172, 2000.
132. KALTENBACH JA, CZAJA JM, AND KAPLAN CR. Changes in the tonotopic map of the dorsal cochlear lesions by exposure to intense sound. *Hear Res* 59: 213–223, 1992.
133. KALTENBACH JA, GODFREY DA, NEUMANN JB, MCCASLIN DL, AFMAN CHE, AND ZHANG DJ. Changes in spontaneous neural activity in the dorsal cochlear nucleus following exposure to intense sound: relation to threshold shift. *Hear Res* 124: 78–84, 1998.
134. KALTENBACH JA AND MCCASLIN DL. Increases in spontaneous activity in the dorsal cochlear nucleus following exposure to high intensity sound: a possible neural correlate of tinnitus. *Auditory Neurosci* 3: 57–78, 1996.
135. KAZEE AM, HAN LY, SPONGR VP, WALTON JP, SALVI RJ, AND FLOOD DG. Synaptic loss in the central nucleus of the inferior colliculus correlates with sensorineural hearing loss in the C57BL/6J mouse model of presbycusis. *Hear Res* 89: 109–120, 1995.
136. KAZEE AM AND WEST NR. Preservation of synapses on principal cells of the central nucleus of the inferior colliculus with aging in the CBA mouse. *Hear Res* 133:98–106, 1999.
137. KIANG NYS, LIBERMAN MC, AND LEVINE RA. Auditory nerve activity in cats exposed to ototoxic drugs and high-intensity sounds. *Ann Otol Rhinol Laryngol* 75: 1–17, 1976.
138. KILGARD MP AND MERZENICH MM. Cortical map reorganization enabled by nucleus basalis activity. *Science* 279: 1714–1718, 1998.
139. KILGARD MP AND MERZENICH MM. Plasticity of temporal information processing in the primary auditory cortex. *Nat Neurosci* 8: 727–731, 1998.
140. KIM J, MOREST DK, AND BOHNE BA. Degeneration of axons in the brainstem of the chinchilla after auditory overstimulation. *Hear Res* 103: 169–191, 1997.
141. KIMURA M AND EGGERMONT JJ. Effect of acute pure tone induced hearing loss on response properties in three auditory cortical fields in cat. *Hear Res* 135: 146–162, 1999.
142. KITZES LM. Some physiological consequences of neonatal cochlear destruction in the inferior colliculus of the gerbil, *Meriones unguiculatus*. *Brain Res* 306: 171–178, 1984.
143. KITZES LM. Anatomical and physiological changes in the brainstem induced by neonatal ablation of the cochlea. In: *Auditory System Plasticity and Regeneration*, edited by Salvi RJ, Henderson D, Fiorino F, and Colletti V. New York: Thieme Medical, 1996, p. 256–274.
144. KITZES LM, KAGEZAMA GH, SEMPLE MN, AND KIL J. Development of ectopic projections from the ventral cochlear nucleus to the superior olivary complex induced by neonatal ablation of the contralateral cochlea. *J Comp Neurol* 353: 341–363, 1995.
145. KITZES LM AND SEMPLE MN. Single-unit responses in the inferior colliculus: effects of neonatal unilateral cochlear ablation. *J Neurophysiol* 53: 1483–1500, 1985.
146. KLINKE R, KRAL A, HEID S, TILLEIN J, AND HARTMANN R. Recruitment of the auditory cortex in congenitally deaf cats by long-term cochlear electrostimulation. *Science* 285: 1729–1733, 1999.
147. KONISHI T, SALT AN, AND HAMRICK PE. Effects of exposure to noise on ion movement in guinea pig cochlea. *Hear Res* 1: 325–342, 1979.
148. KONISHI T, SALT AN, AND HAMRICK PE. Effects of exposure to noise on permeability to potassium of the endolymph-perilymph barrier in guinea pigs. *Acta Otolaryngol* 94: 395–401, 1982.
149. KRAL A, HARTMANN R, TILLEIN J, HEID S, AND KLINKE R. Congenital auditory deprivation reduces synaptic activity within the auditory cortex in a layer-specific manner. *Cereb Cortex* 10: 714–726, 2000.
150. KRAUS N AND DISTERHOFT JF. Response plasticity of single neurons in rabbit auditory association cortex during tone-signaled learning. *Brain Res* 246: 205–215, 1982.
151. KRAUS N, MCGEE T, CARRELL TD, KING C, TREMBLAY K, AND NICOL T. Central auditory system plasticity associated with speech discrimination training. *J Cognitive Neurosci* 7: 25–32, 1995.
152. KRAUS N, MCGE TJ, AND KOCH DB. Speech sound representation, perception, and plasticity: a neurophysiologic perspective. *Audiol Neurotol* 3: 168–182, 1998.
153. KRAUS N, MCGEE TJ, AND KOCH DB. Speech sound perception and learning: biologic bases. *Scand Audiol* 27: 7–17, 1998.
154. KUJAWA SG AND LIBERMAN CM. Conditioning-related protection from acoustic injury: effects of chronic deefferentation and sham surgery. *J Neurophysiol* 78: 3095–3106, 1997.
155. KUJAWA SG AND LIBERMAN CM. Long-term sound conditioning enhances cochlear sensitivity. *J Neurophysiol* 82: 863–873, 1999.
156. KUK FK, TYLER RS, RUSTAD N, HARKER LA, AND TYE-MURRAY N. Alternating current at the eardrum for tinnitus reduction. *J Speech Hear Res* 32: 393–400, 1989.
157. LEAKE PA AND HRADEK GT. Cochlear pathology of long-term neomycin induced deafness in cats. *Hear Res* 33: 11–34, 1988.
158. LEAKE PA, HRADEK GT, REBSCHER SJ, AND SNYDER RL. Chronic intracochlear electrical stimulation induces selective survival of spiral ganglion neurons in neonatally deafened cats. *Hear Res* 54: 251–271, 1991.
159. LEAKE PA, HRADEK GT, AND SNYDER RL. Chronic electrical stimulation by a cochlear implant promotes survival of spiral ganglion neurons after neonatal deafness. *J Comp Neurol* 412: 543–562, 1999.
160. LEAKE PA, SNYDER RL, HRADEK GT, AND REBSCHER SJ. Chronic intracochlear electrical stimulation in neonatally deafened cats. II. Effects of intensity and stimulating electrode location. *Hear Res* 64: 99–117, 1992.
161. LECLERC C, SAINT-AMOUR D, LAVOIE ME, LASSONDE M, AND LEPORE F. Brain functional reorganization in early blind humans revealed by auditory event-related potentials. *Neuroreport* 11: 545–550, 2000.
162. LEHMANN J, NAGY J, ATMADJA S, AND FIBIGER HC. The nucleus basalis magnocellularis: the origin of a cholinergic projection to the neocortex of the rat. *Neuroscience* 5: 1161–1174, 1980.
163. LESPERANCE MM, HELFERT RH, AND ALTSCHULER RA. Deafness induced cell size changes in rostral AVCN of the guinea pig. *Hear Res* 86: 77–81, 1995.
164. LESSARD N, PARE M, LEPORE F, AND LASSONDE M. Early-blind human subjects localize sound sources better than the sighted subjects. *Nature* 395: 278–280, 1998.
165. LI HS. Influence of genotype and age on acute acoustic trauma and recovery in CBA/Ca and C57BL/6J mice. *Acta Otolaryngol* 112: 965–967, 1992.
166. LI HS AND BORG E. Age-related loss auditory sensitivity in two mouse genotypes. *Acta Otolaryngol* 111: 827–834, 1991.
167. LI HS AND HULTCRANTZ M. Age-related degeneration of the organ of Corti in two genotypes of mice. *Otorhinolaryngology* 56: 61–67, 1994.
168. LI L, PARKINS CW, AND WEBSTER DB. Does electrical stimulation of deaf cochleae prevent spiral ganglion degeneration? *Hear Res* 133: 27–39, 1999.
169. LIBERMAN MC AND DODDS LW. Single-neuron labeling and chronic cochlea pathology. III. Stereocilia damage and alterations of threshold tuning curves. *Hear Res* 16: 55–74, 1984.
170. LIBERMAN MC AND KIANG NYS. Trauma in cats: cochlear pathology and auditory nerve activity. *Acta Otolaryngol* 358: 1–63, 1978.
171. LOCKWOOD AH, SALVI RJ, COAD ML, TOWSLEY ML, WACK DS, AND MURPHY BW. The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. *Neurology* 50: 114–120, 1998.
172. LOCKWOOD AH, SALVI RJ, COAD ML, WACK DS, AND MURPHY BW. Neural plasticity in patients with tinnitus and sensorineural hearing loss. In: *Acoustical Signal Processing in the Central Auditory System*, edited by Syka J. New York: Plenum, 1997, p. 529–534.
173. LONSBURY-MARTIN BL AND MARTIN GK. Effects of moderately intense sound on auditory sensitivity in rhesus monkeys: behavioral and neural observations. *J Neurophysiol* 46: 563–586, 1981.
174. LONSBURY-MARTIN BL, MARTIN GK, MCCOY MJ, AND WHITEHEAD ML. New approaches to the evaluation of the auditory system and a current analysis of otoacoustic emissions. *Otolaryngol Head Neck Surg* 112: 50–63, 1995.
175. LOUSTEAU RJ. Increased spiral ganglion cell survival in electrically stimulated, deafened guinea pig cochleae. *Laryngoscope* 97: 836–842, 1987.
176. LUSTIG LR, LEAKE PA, SNYDER RL, AND REBSCHER SJ. Changes in the cat cochlear nucleus following neonatal deafening and chronic intracochlear electrical stimulation. *Hear Res* 74: 29–37, 1994.

177. LUTMAN ME, GATEHOUSE S, AND WORTHINGTON AG. Frequency resolution as a function of hearing threshold level and age. *J Acoust Soc Am* 89: 320–328, 1991.
178. MA X AND SUGA N. Plasticity of bat's central auditory system evoked by focal electric stimulation of auditory and/or somatosensory cortices. *J Neurophysiol* 85: 1078–1087, 2001.
179. MAIR IWS. Hereditary deafness in the white cat. *Acta Otolaryngol Suppl* 314: 1–53, 1973.
180. MALDONADO PE AND GERSTEIN GL. Reorganization in the auditory cortex of the rat induced by intracortical microstimulation: a multiple single-unit study. *Exp Brain Res* 112: 420–430, 1996.
181. MALDONADO PE AND GERSTEIN GL. Neuronal assembly dynamics in the rat auditory cortex during reorganization induced by intracortical microstimulation. *Exp Brain Res* 112: 431–441, 1996.
182. MANUNTA Y AND EDELINE JM. Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow-wave sleep. *Eur J Neurosci* 11: 2134–2150, 1999.
183. MARZELLA PL AND CLARK GM. Growth factors, auditory neurones, and cochlear implants: a rewiew. *Acta Otolaryngol* 119: 407–412, 1999.
184. MATSUSHIMA JI, SHEPHERD RK, SHELDON HL, XU SA, AND CLARK GM. Electrical stimulation of the auditory nerve in deaf kittens: effects on cochlear nucleus morphology. *Hear Res* 56: 133–142, 1991.
185. MATTHIES C AND SAMII M. Management of vestibular schwannomas (acoustic neuromas): the value of neurophysiology for evaluation and prediction of auditory function in 420 cases. *Neurosurgery* 40: 919–929, 1997.
186. MCANALLY KI, CLARK GM, AND SYKA J. Hair cell mediated responses of the auditory nerve to sinusoidal electrical stimulation of the cochlea in the cat. *Hear Res* 67: 55–68, 1993.
187. MCFADDEN SL, CAMPO P, QUARANTA N, AND HENDERSON D. Age-related decline of auditory function in the chinchilla (*Chinchilla laniger*). *Hear Res* 111: 114–126, 1997.
188. MCFADDEN SL AND WILLOTT JF. Responses of inferior colliculus neurons in C57BL/6J mice with and without sensorineural hearing loss: effects of changing the azimuthal location of an unmasked pure-tone stimulus. *Hear Res* 78: 115–131, 1994.
189. MCFADDEN SL AND WILLOTT JF. Responses of inferior colliculus neurons in C57BL/6J mice with and without sensorineural hearing loss: effects of changing the azimuthal location of a continuous noise masker on responses to contralateral tones. *Hear Res* 78: 132–148, 1994.
190. MCGAUGH JL. Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. *Annu Rev Neurosci* 12: 255–287, 1989.
191. MCKENNA TM, ASHE JH, AND WEINBERGER NM. Cholinergic modulation of frequency receptive fields in auditory cortex. I. Frequency-specific effects of muscarinic agonists. *Synapse* 4: 30–43, 1989.
192. MCMULLEN NT, GOLDBERGER B, SUTER CM, AND GLASER EM. Neonatal deafening alters nonpyramidal dendrite orientation in auditory cortex: a computer microscope study in the rabbit. *J Comp Neurol* 267: 92–106, 1988.
193. VON MELCHNER L, PALLAS SL, AND SUR M. Visual behaviour mediated by retinal projections directed to the auditory pathway. *Nature* 404: 871–876, 2000.
194. MERZENICH MM, JENKINS WM, JOHNSTON P, SCHREINER C, MILLER SL, AND TALLAL P. Temporal processing deficits of language-learning impaired children ameliorated by training. *Science* 271: 77–81, 1996.
195. MESULAM MM, MUFSON EJ, LEVEY AI, AND WAINER BH. Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol* 214: 170–197, 1983.
196. METHERATE R AND ASHE JH. Basal forebrain stimulation modifies auditory cortex responsiveness by an action at muscarinic receptors. *Brain Res* 559: 163–167, 1991.
197. METHERATE R AND ASHE JH. Nucleus basalis stimulation facilitates thalamocortical synaptic transmission in the rat auditory cortex. *Synapse* 14: 132–143, 1993.
198. METHERATE R, COX CL, AND ASHE JH. Cellular bases of neocortical activation: modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. *J Neurosci* 12: 4710–4711, 1992.
199. METHERATE R AND WEINBERGER NM. Cholinergic modulation of responses to single tones produces tone-specific receptive field alterations in cat auditory cortex. *Synapse* 6: 133–145, 1990.
200. MIKAELIAN DO. Development and degeneration of hearing in the C57/b16 mouse: relation of electrophysiologic responses from the round window and cochlear nucleus to cochlear anatomy and behavioral responses. *Laryngoscope* 34: 1–15, 1979.
201. MILBRANDT JC, ALBIN RL, AND CASPARY DM. Age-related decrease in $GABA_B$ receptor binding in the Fischer 344 rat inferior colliculus. *Neurobiol Aging* 15: 699–703, 1994.
202. MILBRANDT JC, ALBIN RL, TURGEON SM, AND CASPARY DM. $GABA_A$ receptor binding in the aging rat inferior colliculus. *Neuroscience* 73: 449–458, 1996.
203. MILBRANDT JC AND CASPARY DM. Age-related reduction of [^{3}H]strychnine binding sites in the cochlear nucleus of the Fischer 344 rat. *Neuroscience* 67: 713–719, 1995.
204. MILLER JM, ALTSCHULER RA, DUPONT J, LESPERANCE M, AND TUCCI D. Consequences of deafness and electrical stimulation on the auditory systém. In: *Auditory System Plasticity and Regeneration*, edited by Salvi RJ, Henderson D, Fiorino F, and Colletti V. New York: Thieme Medical, 1996, p. 378–391.
205. MILLER JM, CHI DH, O'KEEFFE LJ, KRUSZKA P, RAPHAEL Y, AND ALTSCHULER RA. Neurotrophins can enhance spiral ganglion cell survival after inner hair cell loss. *Int J Dev Neurosci* 15: 631–643, 1997.
206. MILLS JH, BOETTCHER FA, AND DUBNO JR. Interaction of noise-induced permanent threshold shift and age-related threshold shift. *J Acoust Soc Am* 101: 1681–1686, 1997.
207. MILLS JH, GENGEL RW, WATSON CH, AND MILLER J. Temporary changes of the auditory system due to exposure to noise for one or two days. *J Acoust Soc Am* 2: 524–530, 1970.
208. MILLS JH, SCHMIEDT RA, AND KULISH LF. Age-related changes in auditory potentials of Mongolian gerbil. *Hear Res* 46: 201–210, 1990.
209. MØLLER AR, MØLLER MB, JANNETTA PJ, AND JHO HD. Compound action potentials recorded from the exposed eighth nerve in patients with intractable tinnitus. *Laryngoscope* 102: 187–197, 1992.
210. MONGAN E, KELLY P, NIES K, PORTER WW, AND PAULUS HF. Tinnitus as an indication of therapeutic serum salicylate levels. *J Am Med Assoc* 226: 142–145, 1973.
211. MOORE DR. Auditory brainstem of the ferret: early cessation of developmental sensitivity to cochlear removal in the cochlear nucleus. *J Comp Neurol* 302: 810–823, 1990.
212. MOORE DR. Auditory brainstem of the ferret: early cessation of developmental sensitivity of neurons in the cochlear nucleus to removal of the cochlea. *J Comp Neurol* 303: 2–15, 1990.
213. MOORE DR. Trophic influences of excitatory and inhibitory synapses on neurones in the auditory brainstem. *Neuroreport* 3: 269–272, 1992.
214. MOORE DR. Plasticity of binaural hearing and some possible mechanisms following late-onset deprivation. *J Am Acad Audiol* 4: 277–283, 1993.
215. MOORE DR. Auditory brainstem of the ferret: long survival following cochlear removal progressively changes projections from the cochlear nucleus to the inferior colliculus. *J Comp Neurol* 339: 301–310, 1994.
216. MOORE DR, FRANCE SJ, MCALPINE D, MOSSOP JE, AND VERSNEL H. Plasticity of inferior colliculus and auditory cortex following unilateral deafening in adult ferrets. In: *Acoustical Signal Processing in the Central Auditory System*, edited by Syka J. New York: Plenum, 1997, p. 489–499.
217. MOORE DR, KING AJ, MCALPINE D, MARTIN RL, AND HUTCHINGS ME. Functional consequences of neonatal cochlear removal. *Prog Brain Res* 97: 127–133, 1993.
218. MOORE DR AND KITZES LM. Projections from the cochlear nucleus to the inferior colliculus in normal and neonatally cochlea-ablated gerbils. *J Comp Neurol* 240: 180–195, 1985.
219. MOORE DR AND KITZES LM. Cochlear nucleus lesions in the adult gerbil: effects on neurone responses in the contralateral inferior colliculus. *Brain Res* 373: 268–274, 1986.
220. MOORE DR AND KOWALCHUK NE. Auditory brainstem of the ferret: effects of unilateral cochlear nucleus volume and projections to the inferior colliculus. *J Comp Neurol* 272: 503–515, 1988.
221. MOORE JK, NIPARKO JK, MILLER MR, AND LINTHICUM FH. Effect of

profound hearing loss on a central auditory nucleus. *Am J Otol* 15: 588–595, 1994.
222. MOREST DK AND BOHNE BA. Noise-induced degeneration in the brain and representation of inner and outer hair cells. *Hear Res* 9: 145–151, 1983.
223. MORRIS JS, FRISTON JJ, AND DOLAN RJ. Experience-dependent modulation of tonotopic neural responses in human auditory cortex. *Proc R Soc Lond* 265: 649–657, 1998.
224. MÜHLNICKEL W, ELBERT T, TAUB E, AND FLOR H. Reorganization of auditory cortex in tinnitus. *Proc Natl Acad Sci USA* 95: 10340–10343, 1998.
225. NAGARAJAN S, MAHNCKE H, SALTZ T, TALLAL P, ROBERTS T, AND MERZENICH MM. Cortical auditory signal processing in poor readers. *Proc Natl Acad Sci USA* 96: 6483–6488, 1999.
226. NAITO Y, OKAZAWA H, HONJO I, HIRANO S, TAKAHASHI H, SHIOMI Y, HOJI W, KAWANO M, ISHIZU K, AND YONEKURA Y. Cortical activation with sound stimulation in cochlear implant users demonstrated by positron emission tomography. *Cogn Brain Res* 2: 207–214, 1995.
227. NAITO Y, TATEYA I, FUJIKI N, HIRANO S, ISHIZU K, NAGAHAMA Y, FUKUYAMA H, AND KOJIMA H. Increased cortical activation during hearing of speech in cochlear implant users. *Hear Res* 143: 139–146, 2000.
228. NAKAGAWA H, SATO K, SHIRAISHI Y, KURIYAMA H, AND ALTSCHULER RA. NMDAR1 isoforms in the rat superior olivary complex and changes after unilateral cochlear ablation. *Mol Brain Res* 77: 246–257, 2000.
229. NEVILLE HJ, BAVELIER D, CORINA D, RAUSCHECKER J, KARNI A, LALWANI BRAUN A, CLARK V, JEZZARD P, AND TURNER R. Cerebral organization for language in deaf and hearing subjects: biological constraints and effects of experience. *Proc Natl Acad Sci USA* 95: 922–929, 1998.
230. NI D, SELDON HL, SHEPHERD RK, AND CLARK GM. Effect of chronic electrical stimulation on cochlear nucleus neuron size in normal hearing kittens. *Acta Otolaryngol* 113: 489–497, 1993.
231. NISHIMURA H, DOI K, IWAKI T, HASHIKAWA K, OKU N, TERATANI T, HASEGAWA T, WATANABE A, NISHIMURA T, AND KUBO T. Neural plasticity detected in short- and long-term cochlear implant users using PET. *Neuroreport* 11: 811–815, 2000.
232. NISHIMURA H, HASHIKAWA K, DOI K, IWAKI T, WATANABE Y, KUSUOKA H, NISHIMURA T, AND KUBO T. Sign language "heard" in the auditory cortex. *Nature* 397: 116, 1999.
233. NISHIYAMA N, HARDIE NA, AND SHEPHERD RK. Neonatal sensorineural hearing loss affects neurone size in cat auditory midbrain. *Hear Res* 140: 18–22, 2000.
234. NORDEEN KW, KILLACKEY HP, AND KITZES LM. Ascending auditory projections to the inferior colliculus in the adult gerbil, *Meriones unguiculatus*. *J Comp Neurol* 214: 131–143, 1983.
235. NORENA A, CRANSAC H, AND CHERY-CROZE S. Towards an objectification by classification of tinnitus. *Clin Neurophysiol* 110: 666–675, 1999.
236. OHL FW AND SCHEICH H. Differential frequency conditioning enhances spectral contrast sensitive of units in auditory cortex (field A1) of the alert mongolian gerbil. *Eur J Neurosci* 8: 1001–1017, 1996.
237. OLDS J, DISTERHOF JF, SEGAL M, KORNBLITH CL, AND HIRSH R. Learning centres of rat brain mapped by measuring latencies of conditioned unit responses. *J Neurophysiol* 35: 202–219, 1972.
238. OLESON TD, ASHE JH, AND WEINBERGER NM. Modification of auditory and somatosensory system activity during pupillary conditioning in the paralyzed cat. *J Neurophysiol* 38: 1114–1139, 1975.
239. PALLAS SL, LITTMAN T, AND MOORE DR. Cross-modal reorganization of callosal connectivity without altering thalamocortical projections. *Proc Natl Acad Sci USA* 96: 8751–8756, 1999.
240. PALMER CV, NELSON CT, AND LINDLEY GA. The functionally and physiologically plastic adult auditory system. *J Acoust Soc Am* 103: 1705–1721, 1998.
241. PALOMBI PS AND CASPARY DM. Physiology of the aged Fischer 344 rat inferior colliculus: responses to contralateral monaural stimuli. *J Neurophysiol* 76: 3114–3125, 1996.
242. PALOMBI PS AND CASPARY DM. Responses of young and aged Fischer 344 rat inferior colliculus neurons to binaural tonal stimuli. *Hear Res* 100: 59–67, 1996.
243. PANTEV C, OOSTENVELD R, ENGELIEN A, ROSS B, ROBERTS LE, AND HOKE M. Increased auditory cortical representation in musicians. *Nature* 392: 811–814, 1998.
244. PANTEV C, WOLLBRINK A, ROBERTS LE, ENGELIEN A, AND LUTKENNHONER B. Short-term plasticity of the human auditory cortex. *Brain Res* 842: 192–199, 1999.
245. PARHAM K AND WILLOT DO. Acoustic startle response in young and aging C57BL/6J and CBA/J mice. *Neuroscience* 102: 881–886, 1988.
246. PARVING A, SØRENSEN MB, BECH B, CHRISTENSEN B, AND SØRENSEN MS. Hearing in the elderly >80 year of age. *Scand Audiol* 26: 99–106, 1997.
247. PASIC TR, MOORE DR, AND RUBEL EW. The effects of altered neuronal activity on cell size in the medial nucleus of the trapezoid body and ventral cochlear nucleus of the gerbil. *J Comp Neurol* 348: 111–120, 1994.
248. PASIC TR AND RUBEL EW. Rapid changes in cochlear nucleus cell size following blockade of auditory nerve electrical activity in gerbils. *J Comp Neurol* 283: 474–480, 1989.
249. PEARSON JD, MORRELL CH, GARDON-SALANT S, BRANT LJ, METTER EJ, KLEIN LL, AND FOZARD JL. Gender differences in a longitudinal study of age-associated hearing loss. *J Acoust Soc Am* 97: 1196–1205, 1995.
250. PONTON CW, DON M, EGGERMONT JJ, WARING MD, KWONG B, AND MASUDA A. Auditory system plasticity in children after long periods of complete deafness. *Neuroreport* 8: 61–65, 1996.
251. PONTON CW, DON M, EGERMONT JJ, WARING MD, AND MASUDA A. Maturation of human cortical auditory function: difference between normal-hearing children and children with cochlear implants. *Ear Hear* 17: 430–437, 1996.
252. PONTON CW, EGGERMONT JJ, DON M, WARING MD, KWONG B, CUNNINGHAM J, AND TRAUTWEIN P. Maturation of the mismatch negativity: effect of profound deafness and cochlear implant use. *Audiol Neurootol* 5: 167–185, 2000.
253. PONTON CW, VASAMA JP, TREMBLAY K, KHOSLA D, KWONG B, AND DON M. Plasticity in the adult human central auditory system: evidence from late-onset profound unilateral deafness. *Hear Res* 154: 32–44, 2001.
254. POPELÁŘ J, ERRE J-P, ARAN J-M, AND CAZALS Y. Plastic changes in ipsi-contralateral differences of auditory cortex and inferior colliculus evoked potentials after injury to one ear in the adult guinea pig. *Hear Res* 72: 125–134, 1994.
255. POPELÁŘ J, HARTMANN R, SYKA J, AND KLINKE R. Middle latency responses to acoustical and electrical stimulation of the cochlea in cats. *Hear Res* 92: 63–77, 1995.
256. POPELÁŘ J AND SYKA J. Noise impairment in the guinea pig. II. Changes of single unit responses in the inferior colliculus. *Hear Res* 8: 273–283, 1982.
257. POPELÁŘ J, SYKA J, AND BERNDT H. Effect of noise on auditory evoked responses in awake guinea pig. *Hear Res* 26: 239–247, 1987.
258. POPELÁŘ J, VALVODA J, AND SYKA J. Acoustically and electrically evoked contralateral suppression of otoacoustic emissions in guinea pigs. *Hear Res* 135: 61–70, 1999.
259. POWELL TSP AND ERULKAR SD. Transneuronal cell degeneration in the auditory relay nuclei of the cat. *J Anat (Lond)* 96: 249–268, 1962.
260. VAN PRAAG H, KEMPERMANN G, AND GAGE FH. Neural consequences of environmental enrichment. *Nature Rev Neurosci* 1: 191–198, 2000.
261. PRASHER D AND CANLON B (Editor). *Cochlear Pharmacology and Noise Trauma*. London: Noise Research Network, 1999.
262. PUEL J-L, D'ALDIN C, RUEL J, LADRECH S, AND PUJOL R. Perspectives in inner ear pharmacology and clinical applications. In: *Cochlear Pharmacology and Noise Trauma*, edited by Prasher D and Canlon B. London: Noise Research Network, 1999, p. 1–8.
263. PUEL JL, PUJOL R, TRIBILAC F, LADRECH S, AND EYBALIN M. Excitatory amino acid antagonists protect cochlear auditory neurons from excitotoxicity. *J Comp Neurol* 341: 241–256, 1994.
264. PUEL JL, RUEL J, D'ALDIN CG, AND PUJOL R. Excitotoxicity and repair of cochlear synapses after noise-trauma induced hearing loss. *Neuroreport* 9: 2109–2114, 1998.
265. RAGGIO MW AND SCHREINER CE. Neuronal responses in cat primary auditory cortex to electrical cochlear stimulation. III. Activation patterns in short- and long-term deafness. *J Neurophysiol* 82: 3506–3526, 1999.

266. RAJAN R. Receptor organ damage causes loss of cortical surround inhibition without topographic map plasticity. *Nat Neurosci* 2: 138–143, 1998.
267. RAJAN R AND IRVINE DRF. Absence of plasticity of the frequency map in dorsal cochlear nucleus of adult cats after unilateral partial cochlear lesions. *J Comp Neurol* 399: 35–46, 1998.
268. RAJAN R, IRVINE DRF, WISE LZ, AND HEIL P. Effects of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex. *J Comp Neurol* 338: 17–49, 1993.
269. RAJAN R AND JOHNSTONE BM. Crossed cochlear influences on monaural temporary threshold shifts. *Hear Res* 9: 279–294, 1983.
270. RAJAN R AND JOHNSTONE BM. Residual effects in monaural temporary threshold shifts to pure tones. *Hear Res* 12: 185–197, 1983.
271. RAJAN R AND JOHNSTONE BM. Electrical stimulation of cochlear efferents at the round window decreases auditory desensitization in guinea pigs. I. Dependence on electrical stimulation parameters. *Hear Res* 36: 53–73, 1988.
272. RAJAN R AND JOHNSTONE BM. Electrical stimulation of cochlear efferents at the round window decreases auditory desensitization in guinea pigs. II. Dependence on level of temporary threshold shifts. *Hear Res* 36: 75–88, 1988.
273. RAUSCHECKER JP. Mechanisms of visual plasticity: Hebb synapses, NMDA receptors, and beyond. *Physiol Rev* 2: 587–615, 1991.
274. RAUSCHECKER JP. Auditory cortical plasticity: a comparison with other sensory systems. *Trends Neurosci* 22: 74–80, 1999.
275. RAUSCHECKER JP AND KORTE M. Auditory compensation for early blindness in cat cerebral cortex. *J Neurosci* 13: 4538–4548, 1993.
276. REALE RA, BRUGGE JF, AND CHAN JCK. Maps of auditory cortex in cats reared after unilateral cochlear ablation in the neonatal period. *Dev Brain Res* 34: 281–290, 1987.
277. REBILLARD G, CARLIER E, REBILLARD M, AND PUJOL R. Enhancement of visual responses on the primary auditory cortex of the cat after an early destruction of cochlear receptors. *Brain Res* 129: 162–164, 1977.
278. REBILLARD G, REBILLARD M, AND PUJOL R. Factors affecting the recording of visual-evoked potentials from the deaf cat primary auditory cortex (AI). *Brain Res.* 188: 252–254, 1980.
279. RECANZONE GH, SCHREINER CE, AND MERZENICH MM. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J Neurosci* 13: 87–103, 1993.
280. ROBERTSON D AND IRVINE DRF. Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *J Comp Neurol* 282: 456–471, 1989.
281. ROBINSON K AND GATEHOUSE S. Changes in intensity discrimination following monaural long-term use of a hearing aid. *J Acoust Soc Am* 97: 1183–1190, 1995.
282. RÖDER B, TEDER-SÄLEJÄRVI W, STERR A, RÖSLER F, HILLYARD SA, AND NEVILLE HJ. Improved auditory spatial tuning in blind humans. *Nature* 400: 162–166, 1999.
283. ROE AW, PALLAS SL, HAHM JO, AND SUR M. A map of visual cortex induced in primary auditory cortex. *Science* 250: 818–820, 1990.
284. ROE AW, PALLAS SL, KWON YH, AND SUR M. Visual projections routed to the auditory pathway in ferrets: receptive fields of visual neurons in the primary auditory cortex. *J Neurosci* 12: 3651–3664, 1992.
285. ROMAND R. (Editor). *Development of Auditory and Vestibular Systems*. New York: Academic, 1983.
286. RUSSELL FA AND MOORE DR. Afferent reorganisation within the superior olivary complex of the gerbil: development and induction by neonatal, unilateral cochlear removal. *J Comp Neurol* 352: 607–625, 1995.
287. RYBALKO N AND SYKA J. Susceptibility to noise exposure during postnatal development in rats. *Hear Res* 155: 32–40, 2001.
288. RYUGO DK, ROSENBAUM BT, KIM PJ, NIPARKO JK, AND SAADA AA. Single unit recordings in the auditory nerve of congenitally deaf white cats: morphological correlates in the cochlea and cochlear nucleus. *J Comp Neurol* 397: 532–548, 1998.
289. SAKAI M AND SUGA N. Plasticity of the cochleotopic (frequency) map in specialized and nonspecialized auditory cortices. *Proc Natl Acad Sci USA* 98: 3507–3512, 2001.
290. SALT AN AND KONISHI T. Effects of noise on cochlear potential and endolymph potassium concentration recerded with potassium-selective electrodes. *Hear Res* 1: 343–363, 1979.
291. SALVI RJ, HAMERNIK RP, AND HENDERSON D. Discharge patterns in the cochlear nucleus of the chinchilla following noise induced asymptotic threshold shift. *Exp Brain Res* 32: 301–320, 1978.
292. SALVI RJ, HENDERSON D, FIORINO F, AND COLLETTI V (Editors). *Auditory System Plasticity and Regeneration*. New York: Thieme Medical, 1996.
293. SALVI RJ, HENDERSON D, AND HAMERNIK RP. Auditory fatigue: retrochochlear components. *Science* 190: 486–487, 1975.
294. SALVI RJ, SAUNDERS SS, GRATTON MA, AREHOLE S, AND POWERS N. Enhanced evoked response amplitudes in the inferior colliculus of the chinchilla following acoustic trauma. *Hear Res* 50: 245–258, 1990.
295. SALVI RJ AND WANG J. Evidence for rapid functional reorganization in inferior colliculus and cochlear nucleus. In: *Acoustical Signal Processing in the Central Auditory System*, edited by Syka J. New York: Plenum, 1997, p. 477–488.
296. SALVI RJ, WANG J, AND POWERS N. Rapid functional reorganization in the inferior colliculus and cochlear nucleus after acute cochlear damage. In: *Auditory System Plasticity and Regeneration*, edited by Salvi RJ, Henderson D, Fiorino F, and Colletti V. New York: Thieme Medical, 1996, p. 275–296.
297. SAUNDERS JC, DEAR SP, AND FLOCK Å. Growth of threshold shift in hair-cell stereocilia following overstimulation. *Hear Res* 23: 245–255, 1986.
298. SAUNDERS JC, DEAR SP, AND FLOCK Å. Changes in stereocilia micromechanics following overstimulation in metabolically blocked hair cells. *Hear Res* 24: 217–225, 1986.
299. SCHLAUG G, JANCKE L, HUANG Y, AND STEINMETZ H. In vivo evidence of structural brain asymmetry in musicians. *Science* 267: 699–701, 1995.
300. SCHMIEDT RA, MILLS JH, AND ADAMS JC. Tuning and suppression in auditory nerve fibers of aged gerbils raised in quiet or noise. *Hear Res* 45: 221–236, 1990.
301. SCHMIEDT RA, MILLS JH, AND BOETTCHER FA. Age-related loss of activity of auditory-nerve fibers. *J Neurophysiol* 76: 2799–2803, 1996.
302. SCHNEIDER BA AND HAMSTRA SJ. Gap detection thresholds as a function of tonal duration for younger and older listeners. *J Acoust Soc Am* 106: 371–380, 1999.
303. SCHWABER MK, GARRAGHTY PE, AND KAAS JH. Neuroplasticity of the adult primate auditory cortex following cochlear hearing loss. *Am J Otol* 14: 252–258, 1993.
304. SHARMA J, ANGELUCCI A, AND SUR M. Induction of visual orientation modules in auditory cortex. *Nature* 404: 841–847, 2000.
305. SHEPHERD RK, BAXI JH, AND HARDIE NA. Response of inferior colliculus neurons to electrical stimulation of the auditory nerve in neonatally deafened cats. *J Neurophysiol* 82: 1363–1380, 1999.
306. SHEPHERD RK, MATSUSHIMA J, MARTIN RL, AND CLARK GM. Cochlear pathology following chronic electrical stimulation of the auditory nerve. II. Deafened kittens. *Hear Res* 81: 150–166, 1994.
307. SHONE G, ALTSCHULER RA, MULLER JM, AND NUTTALL AL. The effect of noise exposure on the aging ear. *Hear Res* 56: 173–178, 1991.
308. SILMAN S, GELFAND SA, AND SILVERMAN CA. Late onset auditory deprivation: effects of monaural versus binaural aids. *J Acoust Soc Am* 76: 1357–1362, 1984.
309. SIMPSON GV, KNIGHT RT, BRAILOWSKY S, PROSPERO-GARCIA O, AND SCABINI D. Altered peripheral and brainstem auditory function in aged rats. *Brain Res* 348: 28–35, 1985.
310. SJOSTROM B AND ANNIKO M. Variability in genetically induced age-related impairment of auditory brainstem response thresholds. *Acta Otolaryngol* 109: 353–360, 1990.
311. SNELL KB. Age-related changes in temporal gap detection. *J Acoust Soc Am* 101: 2214–2220, 1997.
312. SNYDER R, LEAKE P, REBSCHER S, AND BEITEL R. Temporal resolution of neurons in cat inferior colliculus to intracochlear electrical stimulation: effects of neonatal deafening and chronic stimulation. *J Neurophysiol* 73: 449–467, 1995.
313. SNYDER RL, REBSCHER SJ, CAO K, LEAKE PA, AND KELLY K. Chronic intracochlear electrical stimulation in the neonatally deafened cat. I. Expansion of central representation. *Hear Res* 50: 7–34, 1990.
314. SNYDER RL, REBSCHER SJ, CAO K, LEAKE PA, AND KELLY K. Chronic

intracochlear electrical stimulation in the neonatally deafened cat. II. Temporal properties of neurons in the inferior colliculus. *Hear Res* 56: 246–264, 1991.
315. Solecki JM and Gerken GM. Auditory temporal integration in the normal-hearing and hearing-impaired cat. *J Acoust Soc Am* 88: 779–785, 1990.
316. Soucek S and Michaels L. *Hearing Loss in the Elderly*. London: Springer-Verlag, 1990.
317. Spongr VP, Flood DG, Frisina RD, and Salvi RJ. Quantitative measures of hair cell loss in CBA and C57BL/6 mice throughout their life spans. *J Acoust Soc Am* 101: 3546–3553, 1997.
318. Stanton SG and Harrison RV. Projections from the medial geniculate body to primary auditory cortex in neonatally deafened cats. *J Comp Neurol* 426: 117–129, 2000.
319. Strouse A, Ashmead DH, Ohde RN, and Grantham DW. Temporal processing in the aging auditory system. *J Acoust Soc Am* 104: 2385–2399, 1998.
320. Suneja SK, Benson CG, and Potashner SJ. Glycine receptors in adult guinea pig brain stem auditory nuclei: regulation after unilateral cochlear ablation. *Exp Neurol* 154: 473–488, 1998.
321. Suneja SK, Potashner SJ, and Benson CG. Plastic changes in glycine and GABA release, and uptake in adult brain stem auditory nuclei after unilateral middle ear ossicle removal and cochlear ablation. *Exp Neurol* 151: 273–288, 1998.
322. Sur M, Angelucci A, and Sharma J. Rewiring cortex: the role of patterned activity in development and plasticity of neuronal circuits. *J Neurobiol* 41: 33–43, 1999.
323. Sur M, Garraghty PE, and Roe AW. Experimentally induced visual projections into auditory thalamus and cortex. *Science* 242: 1437–1441, 1988.
324. Sur M and Leamey CA. Development and plasticity of cortical areas and networks. *Nature Rev Neurosci* 2: 251–262, 2001.
325. Sur M, Pallas SL, and Roe AW. Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex. *Trends Neurosci* 13: 227–233, 1990.
326. Sweetow RW. Cognitive aspects of tinnitus patient management. *Ear Hear* 7: 390–396, 1986.
327. Sweetow RW. The evolution of cognitive-behavioral therapy as an approach to tinnitus patient management. *Int Tinnitus J* 1: 61–65, 1995.
328. Syka J. Experimental models of sensorineural hearing loss—effects of noise and ototoxic drugs on hearing. In: *Progress in Sensory Physiology*. Berlin: Springer-Verlag, 1989, vol. 9, p. 98–170.
329. Syka J (Editor). *Acoustical Signal Processing in the Central Auditory System*. New York: Plenum, 1997.
330. Syka J and Popelář J. Hearing threshold shifts from prolonged exposure to noise in guinea pigs. *Hear Res* 3: 205–213, 1980.
331. Syka J and Popelář J. Noise impairment in the guinea pig. I. Changes in electrical evoked activity along the auditory pathway. *Hear Res* 8: 263–272, 1982.
332. Syka J and Popelář J. Modulation of thresholds to acoustical and electrical stimulation of the intact ear in guinea pig by furosemide and noise. *Hear Res* 75: 1–10, 1994.
333. Syka J, Popelář J. Kvašňák E, and Astl A. Response properties of neurons in the central nucleus and external and dorsal cortices of the inferior colliculus in guinea pig. *Exp Brain Res* 133: 254–266, 2000.
334. Syka J and Rybalko N. Threshold shifts and enhancement of cortical evoked responses after noise exposure in rats. *Hear Res* 139: 59–68, 2000.
335. Syka J, Rybalko N, and Popelář J. Enhancement of the auditory cortex evoked responses in awake guinea pigs after noise exposure. *Hear Res* 78: 158–168, 1994.
336. Szczepaniak WS and Moller AR. Evidence of decreased GABAergic influence on temporal integration in the inferior colliculus following acute noise exposure: a study of evoked potentials in the rat. *Neurosci Lett* 196: 77–80, 1995.
337. Takeda S, Morioka I, Miyashita K, Okumura A, Yoshida Y, and Matsumoto K. Age variation in the upper limit of hearing. *Eur J Appl Physiol* 65: 403–408, 1992.
338. Tallal P, Merzenich MM, Miller S, and Jenkins W. Language learning impairments: integrating basic science, technology, and remediation. *Exp Brain Res* 123: 210–219, 1998.
339. Tallal P, Miller SL, Bedi G, Byma G, Wang X, Nagarajan SS, Schreiner C, Jenkins WM, and Merzenich MM. Language comprehension in language-learning impaired children improved with acoustically modified speech. *Science* 271: 81–84, 1996.
340. Tallal P, Miller S, and Fitch RH. Neurobiological basis of speech: a case for the preeminence of temporal processing. *Ann NY Acad Sci* 682: 27–47, 1993.
341. Tarnowski BI, Schmiedt RA, Hellstrom LI, Lee FS, and Adams JC. Age-related changes in cochleas of Mongolian gerbils. *Hear Res* 54: 123–134, 1991.
342. Temple E, Poldrack RA, Protopapas A, Nagarajan S, Salz T, Tallal P, Merzenich MM, and Gabrieli JD. Disruption of the neural response to rapid acoustic stimuli in dyslexia: evidence from functional MRI. *Proc. Natl Acad Sci USA* 97: 13907–13912, 2000.
343. Temple E, Poldrack RA, Salidis J, Deutsch GK, Tallal P, Merzenich MM, and Gabrieli JD. Disrupted neural responses to phonological and orthographic processing in dyslexic children: an fMRI study. *Neuroreport* 12: 299–307, 2001.
344. Thoenen H. Neurotrophins and neuronal plasticity. *Science* 270: 593–598, 1995.
345. Thoenen H. Neurotrophins and activity-dependent plasticity. In: *Progress in Brain Research*, edited by Seil FJ. Amsterdam: Elsevier, 2000, vol. 128, p. 183–191.
346. Tierney TS, Russell FA, and Moore DR. Abrupt cessation during early postnatal development of afferent dependent survival of gerbil cochlear nucleus neurons. *J Comp Neurol* 378: 295–306, 1997.
347. Trune DR. Influence of neonatal cochlear removal on the development of mouse cochlear nucleus. I. Number, size, and density of its neurons. *J Comp Neurol* 209: 409–424, 1982.
348. Turner JG and Willott JF. Exposure to an augmented acoustic environment alters progressive hearing loss in DBA/2J mice. *Hear Res* 118: 101–113, 1998.
349. Tyler RS. Perspectives on tinnitus. *Br J Audiol* 31: 381–386, 1997.
350. Tyler RS, Aran JM, and Dauman R. Recent advances in tinnitus. *Am J Audiol* 1: 36–44, 1992.
351. Tyler RS, Fryauf-Bertschy H, Gantz BJ, Kelsay DMR, and Woodworth GG. Speech perception in prelingually implanted children after four years. In: *Cochlear Implant and Related Update: Advances in Otorhinolaryngology*, edited by Honjo I and Takahashi H. Basel: Karger, 1997, p. 187–192.
352. Tyler R, Parkinson AJ, Fryauf-Bertchy H, Lowder MW, Parkinson WS, Gantz BJ, and Kelsay DMR. Speech perception by prelingually deaf children and postingually deaf adults with cochlear implant. *Scand Audiol* 26: 65–71, 1997.
353. Tyler RS, Parkinson AJ, Woodworth GG, Lowder MW, and Gantz BJ. Performance over time of adult patients using the ineraid or nucleus cochlear implant. *J Acoust Soc Am* 102: 508–522, 1997.
354. Vasama JP and Makela JP. Auditory pathway plasticity in adult humans after unilateral idiopathic sudden sensorineural hearing loss. *Hear Res* 87: 132–140, 1995.
355. Vasama JP and Makela JP. Auditory cortical responses in humans with profound unilateral sensorineural hearing loss from early childhood. *Hear Res* 104: 183–190, 1997.
356. Wallhäusser-Franke E. Salicylate evokes c-*fos* expression in the brain stem: implications for tinnitus. *Neuroreport* 8: 725–728, 1997.
357. Wallhäusser-Franke E, Braun S, and Langner G. Salicylate alters 2-DG uptake in the auditory system: a model for tinnitus? *Neuroreport* 7: 1585–1588, 1996.
358. Walton JP, Frisina RD, and O'Neill WE. Age-related alteration in processing of temporal sound features in the auditory midbrain of the CBA mouse. *J Neurosci* 18: 2764–2776, 1998.
359. Wang J, Salvi RJ, and Powers N. Plasticity of response properties of inferior colliculus neurons following acute cochlear damage. *J Neurophysiol* 75: 171–183, 1996.
360. Warren R, Tremblay N, and Dykes RW. Quantitative study of glutamic acid decarboxylase-immunoreactive neurones and cytochrome oxidase activity in normal and partially deafferented rat hindlimb somatosensory cortex. *J Comp Neurol* 288: 583–592, 1989.
361. Webster DB. Auditory neuronal sizes after a unilateral conductive hearing loss. *Exp Neurol* 79: 130–140, 1983.
362. Webster DB. Conductive hearing loss affects the growth of the cochlear nuclei over an extended period of time. *Hear Res* 32: 185–192, 1988.

363. WEBSTER DB AND WEBSTER M. Neonatal sound deprivation affects brain auditory nuclei. *Arch Otolaryngol* 103: 392–396, 1977.
364. WEBSTER M AND WEBSTER DB. Spiral ganglion neuron loss following organ of Corti loss. A quantitative study. *Brain Res* 212: 17–30, 1981.
365. WEEKS R, HORWITZ B, AZIZ-SULTAN A, TIAN B, WESSINGER CM, COHEN LG, HALLETT M, AND RAUSCHECKER JP. A positron emission tomographic study of auditory localization in the congenitally blind. *J Neurosci* 20: 2664–2672, 2000.
366. WEINBERGER NM. Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Annu Rev Neurosci* 18: 129–158, 1995.
367. WEINBERGER NM, ASHE JH, DIAMOND DM, METHERATE R, MCKENNA TM, AND BAKIN J. Returning auditory cortex by learning: a preliminary model of receptive field plasticity. *Conc Neurosci* 1: 91–132, 1990.
368. WEINBERGER NM, ASHE JH, METHERATE R, MCKENNA TM, DIAMOND DM, BAKIN JS, LENNARTZ RC, AND CASSADY JM. Neural adaptive information processing: a preliminary model of receptive field plasticity in auditory cortex during Pavlovian conditioning. In: *Neurocomputation and Learning: Foundations of Adaptive Networks*, edited by Gabriel M and Moore J. Cambridge, MA: MIT, 1990, p. 91–138.
369. WEINBERGER NM AND BAKIN JS. Learning-induced physiological memory in adult primary auditory cortex: receptive field plasticity, model, and mechanisms. *Audiol Neurootol* 3: 145–167, 1998.
370. WEINBERGER NM, JAVID R, AND LEPAN B. Long-term retention of learning-induced receptive-field plasticity in the auditory cortex. *Proc Natl Acad Sci USA* 90: 2394–2398, 1993.
371. WEINBERGER NM, JAVID R, AND LEPAN B. Heterosynaptic long-term facilitation of sensory-evoked responses in the auditory cortex by stimulation of the magnocellular medial geniculate body in guinea pigs. *Behav Neurosci* 109: 10–17, 1995.
372. WELKER E, SORIANO E, AND VAN DER LOOS H. Plasticity in the barrel cortex of the adult mouse: effects of peripheral deprivation on GAD-immunoreactivity. *Exp Brain Res* 74: 441–452, 1989.
373. WENNGREN BI AND ANNIKO M. A frequency-specific auditory brainstem response technique exemplified in the determination of age-related auditory thresholds. *Acta Otolaryngol* 106: 238–243, 1988.
374. WEST CD AND HARRISON JM. Transneuronal cell atrophy in the congenitally deaf white cat. *J Comp Neurol* 151: 377–398, 1973.
375. WIESEL TN. Postnatal development of the visual cortex and the influence of environment. *Nature* 299: 583–591, 1982.
376. WIESEL TN AND HUBEL DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 26: 1003–1017, 1963.
377. WILLOTT JF. Changes in frequency representation in the auditory system of mice with age-related hearing impairment. *Brain Res* 309: 159–162, 1984.
378. WILLOTT JF. Effects of aging, hearing loss, and anatomical location on thresholds of inferior colliculus neurons in C57BL/6 and CBA mice. *J Neurophysiol* 56: 391–408, 1986.
379. WILLOTT JF. *Aging and the Auditory System: Anatomy, Physiology, and Psychophysics*. San Diego, CA: Singular, 1991.
380. WILLOTT JF. Anatomic and physiologic aging: a behavioral neuroscience perspective. *J Am Acad Audiol* 7: 141–151, 1996.
381. WILLOTT JF. Auditory system plasticity in the adult C57BL/6J mouse. In: *Auditory System Plasticity and Regeneration*, edited by Salvi R, Henderson D, Fiorino F, and Colletti V. New York: Thieme, 1996, p. 297–316.
382. WILLOTT JF, AITKIN LM, AND MCFADDEN SL. Plasticity of auditory cortex associated with sensorineural hearing loss in adult C57BL/6J mice. *J Comp Neurol* 329: 402–411, 1993.
383. WILLOTT JF, BROSS LS, AND MCFADDEN LS. Morphology of the dorsal cochlear nucleus in young and aging C57BL/6J and CBA/J mice. *J Comp Neurol* 321: 666–678, 1992.
384. WILLOTT JF, BROSS LS, AND MCFADDEN SL. Morphology of the inferior colliculus in C57BL/6J and CBA/J mice across the lifespan. *Neurobiol Aging* 15: 175–183, 1994.
385. WILLOTT JF, CARLSON S, AND CHEN H. Prepulse inhibition of the startle response in mice: relationship to hearing loss and auditory system plasticity. *Behav Neurosci* 108: 703–713, 1994.
386. WILLOTT JF, ERWAY LC, ARCHER JR, AND HARRISON DE. Genetics of age-related hearing loss in mice. II. Strain differences and effects of caloric restriction on cochlear pathology and evoked response thresholds. *Hear Res* 88: 143–155, 1995.
387. WILLOTT JF, JACKSON LM, AND HUNTER KP. Morphometric study of the anteroventral cochlear nucleus of two mouse models of presbycusis. *J Comp Neurol* 260: 472–480, 1987.
388. WILLOTT JF, PARHAM K, AND HUNTER KP. Response properties of inferior colliculus neurons in young and very old CBA/J mice. *Hear Res* 37: 1–14, 1988.
389. WILLOTT JF, PARHAM K, AND HUNTER KP. Response properties of inferior colliculus neurons in middle-aged C57 mice with presbycusis. *Hear Res* 37: 15–28, 1988.
390. WILLOTT JF, PARHAM K, AND HUNTER KP. Comparison of the auditory sensitivity of neurons in the cochlear nucleus and inferior colliculus neurons of young and aging C57BL/6J and CBA/J mice. *Hear Res* 53: 78–94, 1991.
391. WILLOTT JF AND TURNER JG. Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. *Hear Res* 135: 78–88, 1999.
392. WILLOTT JF, TURNER JG, AND SUNDIN VS. Effects of exposure to an augmented acoustic environment on auditory function in mice: roles of hearing loss and age during treatment. *Hear Res* 142: 79–88, 2000.
393. WITHINGTON-WRAY DJ, BINNS KE, DHANJAL SS, BRICKLEY SG, AND KEATING MJ. The maturation of the superior collicular map of auditory space in the guinea pig is disrupted by developmental auditory deprivation. *Eur J Neurosci* 2: 693–703, 1990.
394. WITHINGTON-WRAY DJ, BINNS KE, AND KEATING MJ. A four-day period of bimodality auditory and visual experience is sufficient to permit normal emergence of the map of auditory space in guinea pig superior colliculus. *Neurosci Lett* 116: 280–286, 1990.
395. WONG D, MIYAMOTO RT, PISONI DB, SEHGAL M, AND HUTCHINS GD. PET imaging of cochlear-implant and normal-hearing subjects listening to speech and nonspeech. *Hear Res* 132: 34–42, 1999.
396. WONG TP, CAMPBELL PM, RIBEIRO-DA-SILVA A, AND CUELLO AC. Synaptic numbers across cortical laminae and cognitive performance of the rat during ageing. *Neuroscience* 84: 403–412, 1998.
397. WOODS DL AND CLAYWORT CC. Age-related changes in human middle latency auditory evoked potentials. *Electroencephalogr Clin Neurophysiol* 65: 297–303, 1986.
398. WOODY CD, SWARTZ BE, AND GRUEN E. Effects of acetylcholine and cyclic GMP on input resistance of cortical neurons in awake cats. *Brain Res* 158: 373–395, 1978.
399. WRIGHT H. The effect of sensorineural hearing loss on threshold-duration functions. *J Speech Lang Hear Res* 11: 842–852, 1968.
400. YAKA R, YINON U, AND WOLLBERG Z. Auditory activation of cortical visual areas in cats after early visual deprivation. *Eur J Neurosci* 11: 1301–1312, 1999.
401. YOST WA. Overview: psychoacoustics. In: *Human Psychophysics*, edited by Yost WA, Popper AN, and Fay RR. Berlin: Springer-Verlag, 1993, p. 1–12.
402. ZAPPIA JJ AND ALTSCHULER RA. Evaluation of the effect of ototopical neomycin on spiral ganglion cell density in the guinea pig. *Hear Res* 40: 29–38, 1989.
403. ZETTEL ML, FRISINA RD, HAIDER SE, AND O'NEILL WE. Age-related changes in calbindin D-28k and calretinin immunoreactivity in the inferior colliculus of CBA/CaJ and C57B1/mice. *J Comp Neurol* 386: 92–110, 1997.
404. ZHENG XY, HENDERSON D, MCFADDEN SL, AND HU BH. The role of the cochlear efferent system in acquired resistance to noise-induced hearing loss. *Hear Res* 104: 191–203, 1997.