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Consequences of Deafness and Electrical Stimulation on the Peripheral and Central Auditory System

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Cochlear implants provide important auditory cues necessary for auditory awareness and speech perception in severe to profoundly deaf subjects. Over the past three decades more than 80,000 adults and children worldwide have received these devices. Clinical experience has shown, however, a large variability in outcome among implant users. Factors predicting a successful clinical outcome reflect the importance of auditory experience—either before an acquired hearing loss or with use of a cochlear implant. Moreover, deaf children, with little or no prior auditory experience, can obtain significant benefit from a cochlear implant provided that their device is fitted at a young age. This clinical experience suggests that such a response can be at least partially attributed to plasticity within the auditory system.

This chapter reviews the response of the auditory system to both deafness and its reactivation through a cochlear implant, and includes experimental data from animal models as well as human material where applicable. Understanding the complexities of this response will help provide a substrate for understanding the clinical variability evident among cochlear implant users.

◆ The Cochlea

Cochlear Pathophysiology Following Deafness

Spiral ganglion neurons (SGNs), whose cell bodies are located within Rosenthal's canal (**Fig. 3–1**), are the target neurons for cochlear implants. These devices electrically depolarize local populations of SGNs, initiating the generation of action potentials via an electrode array

typically located in the scala tympani (a description of the initiation of an action potential via an electrical stimulus is provided elsewhere¹). It is important to emphasize that once the action potential has been initiated, the implant plays no further role in its propagation along the ascending auditory pathway; saltatory conduction along the central process of the SGN and its passage across synapses within the cochlear nucleus (CN) or higher auditory centers are performed via normal physiologic processes.

Survival of these neurons is dependent on the integrity of the organ of Corti; SGNs are subject to atrophic and degenerative changes that occur secondary to a sensorineural hearing loss (SNHL). Although the minimum number of SGNs required to achieve acceptable clinical performance with a cochlear implant is unclear, the greater number of viable SGNs available for stimulation is likely to result in improved clinical performance.^{2,3} Here we discuss the pathophysiologic changes that occur to the cochlea following SNHL and describe techniques that may lead to SGN preservation.

Cochlear Pathology

Hair cells of the organ of Corti are sensitive to many forms of pathologic damage including acoustic trauma, ototoxic drugs, congenital abnormalities, and aging. Unlike avian hair cells, mammalian hair cells cannot spontaneously regenerate; loss of hair cells results in a permanent SNHL. Several atrophic and pathologic changes occur to SGNs following the loss of the sensory epithelium and the support cells of the organ of Corti. First, there is a rapid

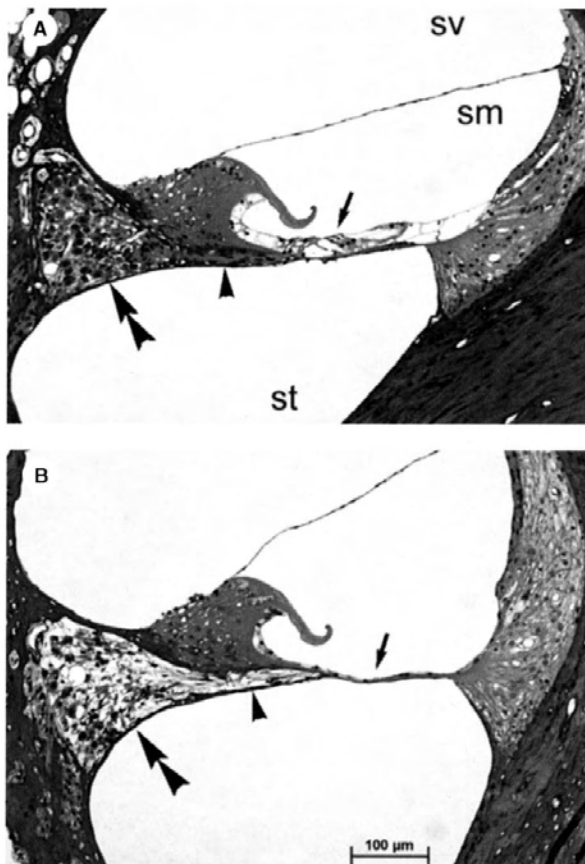


Figure 3-1 Photomicrographs of the upper basal turn from (A) normal hearing and (B) 10-week deafened rat cochleae. The normal organ of Corti evident in the control animal contrasts with the complete degeneration of both hair cells and their supporting structure in the deafened cochlea (arrow). Other deafness-induced degenerative changes evident here include a loss of peripheral processes that would normally innervate the organ of Corti (arrowhead), and loss of the spiral ganglion neuron (SGN) soma within Rosenthal's canal (double arrowhead). sv, scala vestibuli; sm, scala media; st, scala tympani.

and extensive loss of the unmyelinated peripheral processes within the organ of Corti.⁴ This process is followed by a more gradual degeneration of the myelinated portion of the peripheral processes within the osseous spiral lamina and of the cell bodies within Rosenthal's canal⁵⁻⁷ (Fig. 3-1). The degenerative process also results in demyelination of residual SGN soma and possibly part of their central processes.^{5,7,8} Finally, the perikaryon of residual SGNs undergoes considerable shrinkage,⁹⁻¹¹ a response that is repeated throughout the central auditory pathway following an SNHL (see below), although the functional effects of this atrophy are unknown.

The secondary degeneration of SGNs following loss of the organ of Corti is an ongoing process, eventually resulting in very small numbers of surviving neurons^{6,7} (Fig. 3-2). As we will describe below, these pathologic changes affect the physiologic response of SGNs to an electrical stimulus. The ongoing degeneration of SGNs has been widely reported across mammalian species following various etiologies that

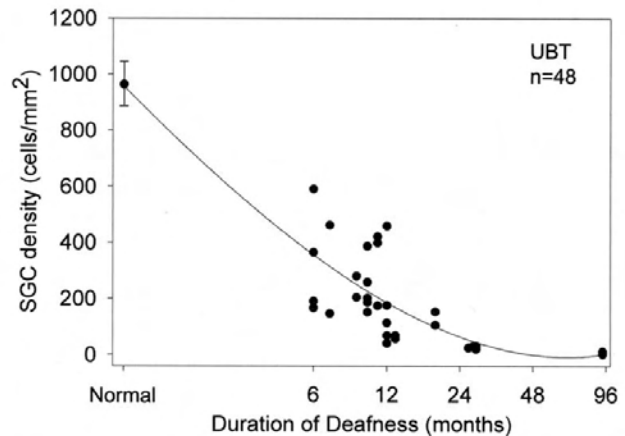


Figure 3-2 Graph illustrating the rate of loss of SGNs in the upper basal turn (UBT) of the cat cochlea as a function of duration of deafness. Although there is a relatively wide individual variability in the data, there is a clear reduction in SGN survival with increased durations of deafness. Similar degenerative patterns are observed in other mammals albeit at different rates. Although rodents such as guinea pigs exhibit a more rapid loss of SGNs compared with the cat, it is important to emphasize that ganglion cell loss is significantly slower in humans. These data are based on counts from 48 cat cochleae including 16 normal hearing controls. Error bar = ± 1 SEM.

target the organ of Corti: mouse,¹² rat,^{13,14} chinchilla,¹⁵ guinea pig,¹⁶ and cat.^{6,7,17-21} It is important to emphasize that the rate of SGN degeneration exhibits considerable variation across species—a theme we shall return to when discussing SGN loss in humans.

In the majority of forms of SNHL, SGN degeneration is secondary to the loss of hair cells and support cells of the organ of Corti.²²⁻²⁴ These changes appear due, at least in part, to the withdrawal of neurotrophic factors normally expressed by the hair cells²⁵⁻²⁸ and nerve growth factors released by support cells.²⁹ This pathway of SGN loss is common to many forms of SNHL described clinically, and would be expected to result in a gradual but ongoing secondary degeneration of SGNs as reported above. Importantly, etiologies that directly target SGNs, including viral and bacterial labyrinthitis, mechanical trauma, and disruption to cochlear vasculature, are likely to result in a more rapid and extensive loss of auditory neurons.

Reports of degeneration patterns of SGNs in human cochleae following a profound SNHL are generally consistent with the experimental studies already summarized. Degeneration of peripheral processes is more extensive than that of the SGN soma or central processes, and the extent of the pathology typically varies with distance along the cochlear partition in a manner that reflects the extent of damage to the organ of Corti, being most extensive in the basal turn with less extensive pathology apicalward.^{3,22,23,30-33}

Analysis of SGN survival from profoundly deaf adult temporal bones reveals a moderate to severe loss of auditory neurons. Otte and colleagues³² studied 62 profoundly deaf ears and demonstrated that 45% of cochleae had a SGN population in excess of 10,000, that is, approximately one

third of normal ($28,418 \pm 3,675^3$). Nadol and colleagues³ studied 66 profoundly deaf ears and showed that the mean SGN population was approximately half that of normal ears, although the standard deviation, as in all studies of this sort, was large ($14,061 \pm 8,063$). Total SGN loss tended to be greater in older compared with younger subjects and, consistent with animal studies, greater loss was observed with longer durations of deafness. However, the single most significant determinant of SGN loss in humans was etiology,^{3,31} with loss most extensive in patients with postnatal viral labyrinthitis, congenital or genetic deafness, or bacterial meningitis, that is, pathologies that directly target SGNs or patients having long durations of deafness. Patients deafened with aminoglycoside antibiotics or sudden idiopathic deafness typically exhibited the smallest levels of SGN pathology.

Although many of the findings observed in adult temporal bones have also been reported in temporal bones from profoundly deaf children, two important differences were noted: (1) the SGN population in children did not show evidence of ongoing loss with duration of deafness within the age range of 0 to 9 years; and (2) there was a more even distribution of SGNs throughout the cochleae.³⁴ These results provide encouraging findings for pediatric cochlear implantation, and emphasize the relatively slow rate of SGN degeneration evident in humans compared with experimental animals. This situation may reflect, at least in part, the lack of a long-term decrease in clinical performance with device use.³⁵

Physiologic Response of the Spiral Ganglion Neuron to Deafness

Despite the extensive pathologic changes that occur to SGNs following an SNHL, these neurons remain capable of initiating and propagating action potentials elicited via an electrical stimulus, even in cochleae deafened for many years, with surviving neural populations of <5% of normal.⁶ In general, the basic response properties of SGNs in deafened cochleae remain similar to those observed in normal cochleae; that is, the cells show an increase in the probability of firing and a decrease in both response latency and the jitter in the timing of the response with increasing stimulus current. There are, however, more subtle changes seen in neural response properties in cochleae subjected to long periods of deafness; these pathology-induced changes have the potential to degrade the perceptual quality of cochlear implants. First, loss of peripheral process and ongoing loss of SGNs results in an increase in threshold.^{14,36–38} This change likely has an adverse effect on power consumption and results in a reduction in spatial selectivity of the electrode array.³⁹ Second, demyelination results in an increase in membrane capacitance,^{40,41} reducing the efficiency of a neuron in initiating and propagating action potentials in response to electrical stimuli. In the auditory system, there is evidence of reduced temporal resolution in myelin-deficient or deafened cochleae,⁴² as well as a significant increase in the refractory properties of auditory nerve fibers¹⁴ and evidence of conduction block.¹⁷

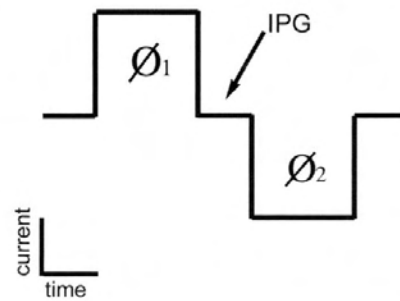


Figure 3–3 Schematic diagram illustrating the charge balanced biphasic current pulses typically used in cochlear implants. Charge in the second phase (Θ_2) is equal in magnitude but opposite in polarity to the charge in the first phase (Θ_1). The duration of each phase typically varies between ~ 10 and $50 \mu\text{s}$ /phase for monopolar stimulation and 50 and $200 \mu\text{s}$ /phase for the less efficient bipolar stimulation. IPG, interphase gap.

Effects of Electrical Stimulation

Safety Issues

Nondamaging electrical stimulation consists of short-duration (<200 μs /phase) charge-balanced biphasic current pulses (Fig. 3–3) delivered using platinum electrodes and operating at charge densities of <60 $\mu\text{C}/\text{cm}^{-2}$ geom per phase.^{43–49} These stimulus guidelines ensure that the charge injection process is achieved using reversible electrochemical reactions localized to the electrode–tissue interface, minimizing the chance of releasing potentially harmful electrochemical products into the tissue environment.^{50–52} Contemporary cochlear implants operating in a monopolar electrode configuration would typically produce charge densities of an order of magnitude below these levels.

Although theoretically, charge-balanced biphasic current pulses should not result in the production of potentially damaging direct current, in practice it is not possible to generate perfectly balanced stimuli. Neural damage and new bone formation is observed following chronic stimulation with direct current levels greater than $0.4 \mu\text{A}$.^{53,54} Protection against direct current, and the local pH changes that occur as a result of charge imbalance, can be achieved by either shorting electrodes between current pulses or by placing a capacitor in series with each electrode.^{55,56} One or a combination of these techniques is used to ensure complete charge recovery in contemporary cochlear implant systems.

Trophic Effects of Electrical Stimulation on Spiral Ganglion Neuron Survival

In deafness, there is a lack of both driven neural activity and significant reductions in the levels of spontaneous activity,^{17,20,21,37} such that SGNs rarely undergo depolarization. However, neural activity is known to play an important role in SGN survival; depolarization is sufficient to maintain neuronal survival in vitro without the addition of neurotrophic factors.⁵⁷ Membrane depolarization

appears to promote SGN survival by elevating intracellular calcium levels and cascading several intracellular signaling pathways.⁵⁷ Finally, the trophic support of SGNs via depolarization *in vitro* appears to be additive with the actions of some neurotrophins.⁵⁸

Several *in vivo* studies have described significant increases in SGN survival—to levels of up to 70% greater than non-stimulated control cochleae—in ototoxically deafened animals following chronic electrical stimulation of the auditory nerve.^{59–67} However, it is important to emphasize that this is not a universal finding; work from other laboratories has reported no such trophic influence.^{43,45,68,69} Given the subtle methodological differences across studies, this variation in results is not surprising. Indeed, it is expected that these differences will ultimately provide further insight into the mechanisms underlying stimulus-induced trophic support of SGNs.

There is agreement, however, that chronic electrical stimulation in deafened ears results in subtle morphologic changes to SGNs. For example, there is a small but significant increase in the soma area of SGNs in deafened, chronically stimulated cochleae compared with deafened controls.^{43,67} This increase in soma area presumably reflects an increase in biosynthetic activity within the SGN soma following reactivation via an electrical stimulus.

Neurotrophin Support of the Spiral Ganglion

Several growth factor families have been shown to play important roles in the development, maintenance, and protection against injury of SGNs.⁷⁰ Both presynaptic hair cells and postsynaptic neurons within the CN are necessary for SGN survival, reflecting complementary neurotrophic support from both sources. These neurotrophins include both brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3)^{25,26,71}, with receptors for both of

these neurotrophins expressed on SGNs.^{25,26} Moreover, survival of SGNs in the absence of hair cells has been promoted by exogenous BDNF or NT-3 *in vivo*.^{13,16,72–74}

This research has recently been extended to demonstrate enhanced SGN survival in deafened cochleae treated with both exogenous neurotrophins and electrical stimulation^{63,69} (Fig. 3–4). Importantly, this work has also shown a functional advantage, in the form of significantly reduced electrically evoked auditory brainstem response thresholds in ears treated with neurotrophins,^{69,75} that may be associated with a neurotrophin-mediated growth of SGN peripheral processes toward the scala tympani.^{74,76} Reductions in electrical thresholds would reduce the power consumption of a cochlear implant, thereby providing several engineering advantages including the possibility of smaller, more numerous electrode contacts.

Although these results are promising, from a clinical perspective further research is necessary before neurotrophins can be combined with cochlear implants. First, the long-term safety and efficacy of neurotrophin delivery to the cochlea must be examined, as there is evidence that the removal of exogenous BDNF leads to an accelerated loss of SGNs,⁷⁷ implying that the neurotrophin must be supplied continuously. The perilymph of scala tympani is connected to the cerebrospinal fluid via the cochlear aqueduct; therefore, safety studies must be directed at both the level of the cochlea and the central nervous system (CNS). Second, an appropriate strategy for long-term delivery of neurotrophins must be established. The use of pumps should be discouraged because of the risks of introducing infection into the inner ear. Alternative delivery methods using viral vectors or cell-based therapies hold promise in this area.⁶³ Finally, while neurotrophin therapy has been shown to protect SGNs following an insult to the organ of Corti, it is not clear whether neurotrophins would be effective in etiologies that directly target SGNs.

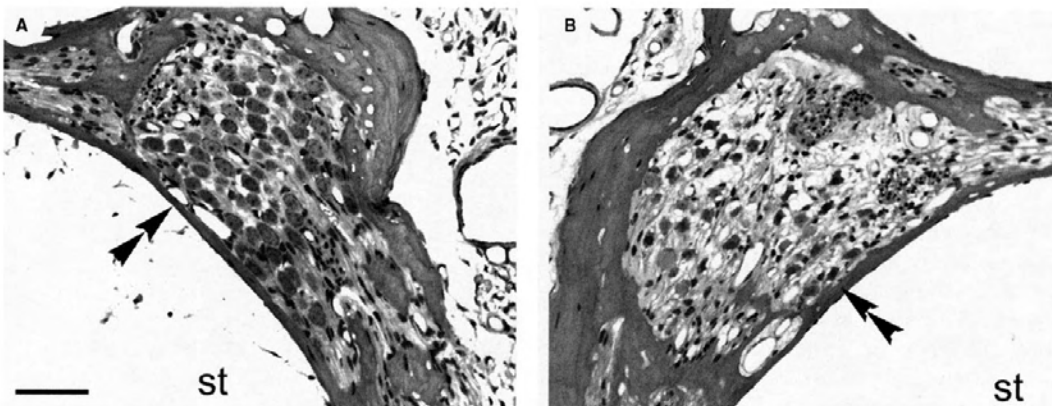


Figure 3–4 Photomicrographs of Rosenthal's canal (double arrowhead) and the SGNs of the upper basal turn from deafened guinea pig cochleae (A) treated with the neurotrophin brain-derived neurotrophic factor (BDNF) and electrically stimulated via a cochlear

implant and (B) the contralateral deafened untreated control. The near-normal SGN population in the BDNF-treated cochlea contrasts with the ~50% SGN loss after 4 weeks of deafening in the deafened control cochlea. st, scala tympani. Scale bar = 50 μ m.

◆ The Cochlear Nucleus

Deafness and the Cochlear Nucleus

The role of acoustically generated activity on the structural and functional development of the central auditory system is a subject of intense research. Auditory deprivation in the developing animal produces severe abnormalities in the central pathway, whereas older animals are less affected.^{78–84} Postmortem studies of those rare human cases where the profound hearing loss of the individual is documented has revealed up to 50% somatic shrinkage in the CN, with acknowledgment that many variables contribute to the nonuniform results.^{85–88} Clinical observations related to congenital deafness suggest that the best candidates for cochlear implants are very young children, and that with increasing age the outcomes become less optimal.^{89–91} The implication is that sensory stimulation, whether natural or prosthetic, is necessary during early life to ensure the normal development of the central auditory system.

In the auditory system, there is a period during which the normal development of speech and hearing is adversely affected by sound deprivation, and thereafter it cannot be remedied even if sound is fully restored. The nature of this epoch, called the “critical period,” is conceptually similar across species but undoubtedly varies in timing and magnitude of effect. Intervention strategies in the case of pediatric patients with a profound SNHL have concentrated on cochlear implants, and there is a growing tendency to implant deaf children at earlier and earlier ages. It seems necessary, however, to acquire better knowledge of those factors affecting the structure and function of the auditory system when electrical stimulation is used.

In an effort to understand the influence of acoustic stimulation on the developing brain, there have been experimental manipulations on the end organs to deprive the system of input. Deafening has been produced by surgical or pharmacologic manipulations of the auditory periphery as well as by congenital or hereditary defects. Each form of deafness is accompanied by its own potential complication. One must be vigilant for indirect surgical trauma, nonspecific drug effects, and downstream genetic influences.

Models of Deafness and the Cochlear Nucleus

The least invasive manipulation on the auditory system is produced by the introduction of conductive hearing loss. This method basically involves the “plugging” of the ear canal with a malleable substance or removing one of the ossicles. Results from ear plugging have been inconsistent, probably because of the high rates of spontaneous discharges in auditory nerve fibers, which are not affected by this manipulation.⁹² Even with extreme plugging strategies, the effects are relatively small and show signs of recovery.^{93–95}

Surgical ablation of the cochleae in neonatal animals produces a profound SNHL and results in ~50% ipsilateral volume loss, 30 to 40% cell body shrinkage, and >50% neural death in the CN.^{81,96,97} Importantly, the loss of central neurons following cochlear ablation is restricted to

a critical period that appears to end at the onset of hearing.^{98,99} Although deafferentation during cochlear development results in widespread neural loss in the CN, similar cochlear damage after the onset of hearing results in atrophic changes but not neural loss. Given that most forms of SNHL occur following the onset of hearing,^{100–102} these results imply that the major transneuronal effects of deafness are atrophic, with relatively small amounts of neural loss.

An alternative form of deafening is provided by the administration of ototoxic drugs. These drugs (e.g., amikacin, neomycin, kanamycin, ethacrynic acid) are known to cause a loss of hair cell receptors and deafness^{7,103–105} as described above. Following ganglion cell loss, there is a reduction in CN volume and distinct cell shrinkage in cats, gerbils, and guinea pigs,^{6,106–108} with the effect on the ventral CN much greater compared with that on the dorsal CN. This form of deafening represents the model of choice for current investigations of this topic.

The congenitally deaf white cat (DWC) represents a third alternative for these kinds of studies.^{19,20,82,109–114} DWCs have long been of interest because an autosomal dominant gene links coat color, eye pigment, and deafness.^{115–119} This well-documented syndrome is probably a variably penetrant and variably expressive syndrome affecting several characteristics including cochlear pathology¹²⁰ that was first described in congenitally deaf patients.^{121,122} The pathology in the DWC ranges from moderate hair cell loss to complete collapse of the organ of Corti with corresponding degrees of hearing loss.^{19,20,110,123–125} For those animals with a profound SNHL, deafness is manifest by the collapse of Reissner's membrane onto the undifferentiated organ of Corti, thinning of the stria vascularis, and malformation of the tectorial membrane. A variable degree of SGN degeneration proceeds over time,^{118,124} and distinct atrophic features are evident in the CN including a 50% reduction in nuclear volume and a differential shrinkage of separate cell types.^{20,109,126,127} Furthermore, a hypertrophy of synapses is seen on some but not other CN neurons.⁸² Spherical and globular bushy cells represent two major cell classes in the ventral CN. Spherical bushy cells receive large axosomatic endings called endbulbs of Held, whereas globular bushy cells received smaller endbulbs. Congenital deafness results in a reduction in endbulb branching, reduction of presynaptic vesicles, flattening and hypertrophy of postsynaptic densities, and loss of intermembranous channels. Synapses on spherical bushy cells are severely affected by a SNHL, whereas those on globular bushy cells are less so. In contrast, synapses on multipolar cells exhibit only slight structural abnormalities^{82,113,128} (Fig. 3–5).

The structural abnormalities in CN neurons in response to a SNHL seem a natural consequence of abnormal inputs from the auditory nerve. Congenital and ototoxic deafness significantly reduces the levels of spontaneous activity in auditory nerve fibers of the cat.^{17,20} Variations in spontaneous activity in auditory nerve fibers have an effect on spherical bushy cells even in normal hearing cats.¹²⁹ Deafness-induced changes are expressed as increased thresholds to activation,¹⁴ smaller action potentials, smaller after-hyperpolarizations, and shorter membrane time constants.¹³⁰

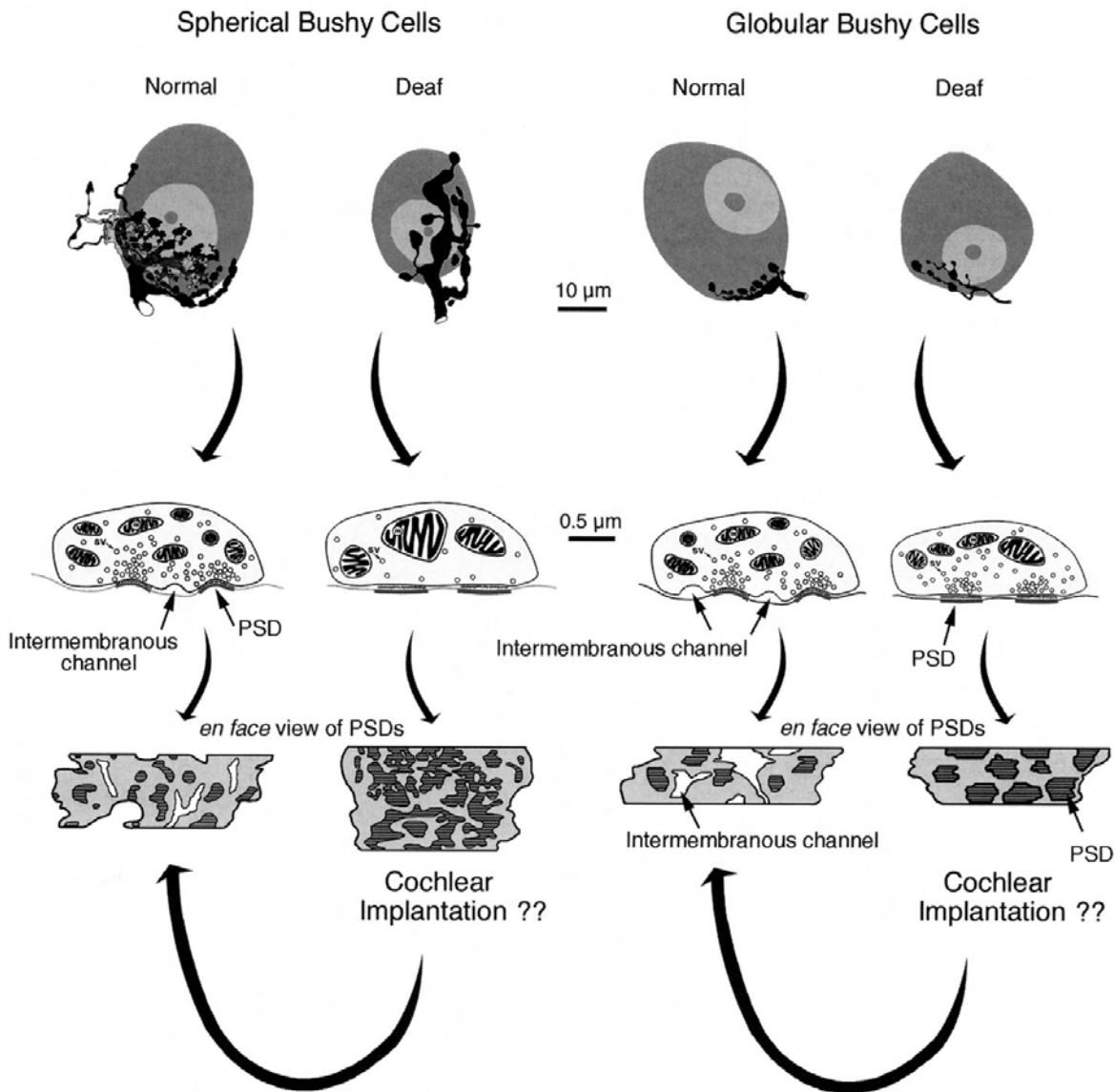


Figure 3-5 Schematic diagram summarizing the effects of deafness on bushy cells of the cochlear nucleus (CN). Congenital deafness results in shrinkage of the bushy cell body, a reduction in endbulb branching, reduction of presynaptic vesicles, flattening and hypertrophy of postsynaptic densities, and loss of intermembranous channels. Although globular bushy cells show similar deafness-induced changes, they are not as extensive as those observed in the spherical bushy cell. The question is whether neural activity induced by

cochlear implantation can reverse or reduce these abnormalities. PSD, postsynaptic density. (Adapted from Redd EE, Pongstaporn T, Ryugo DK. The effects of congenital deafness on auditory nerve synapses and globular bushy cells in cats. *Hear Res* 2000;147:160–174.) *Note:* Recent observations demonstrated that cochlear implantation in young kittens prevented the formation of abnormal auditory nerve synapses (Ryugo et al, *Science* 310:1490–1492, 2005).

Effects of Electrical Stimulation

The question naturally arises as to whether electrical stimulation of the auditory nerve can effectively prevent, ameliorate, or reverse the deleterious effects of deafness. Inherent to the interpretation of implantation and stimulation results is a consideration that either or both manipulations can contribute to changes additional to those caused by SNHL, and the nature of these changes is not necessarily predictable. Nevertheless, given the notion of a “critical period” in auditory system development, deafened animals are being used to develop experimental models. Furthermore, children, especially prelingually deaf children, are postulated

to receive additional benefit from early electrical stimulation via cochlear implants. The rationale is that the preservation of neurons and synapses represents the substrate for improved development of language skills.

The results of electrical stimulation of the auditory nerve on CN structure have not been uniform. In deafened guinea pigs, chronic electrical stimulation of one cochlea resulted in an increase in the size of octopus cells in the ipsilateral CN compared with those on the contralateral side.¹³¹ If specific cell types were not considered, analysis of all neurons suggested that there was no effect of electrical stimulation. Likewise, there was no statistically significant

difference in nuclear volume between the ipsilateral and contralateral sides. In a similar study using unilateral electrical stimulation of ototoxically deafened cats, the size of spherical bushy cells was reduced 20% by deafening, but stimulation did not produce any difference between the ipsilateral and contralateral sides.¹³² In related studies, these same comparisons revealed a small (6%) but statistically significant increase in somatic cross-sectional area between ipsilateral and contralateral spherical bushy cells.^{106,133} There were also mixed results regarding difference in volumes of the cochlear nuclei and somatic sizes of various cell types in the stimulated and non-stimulated sides. Finally, no work has yet examined the effects of chronic electrical stimulation of the auditory nerve on ultrastructural changes to endbulb synapses on spherical or globular bushy cells in the anteroventral CN (Fig. 3–5).

The conclusion from these observations is that electrical stimulation of the cochlea in deaf animals exerts, at best, a small increase in cell body size for CN neurons. There are, however, several considerations that temper this interpretation. First, it isn't always clear that the cells sampled were those that were stimulated. Because the stimulating electrodes are placed in the basal (high frequency) end of the cochlea, the sampling must also occur in the high-frequency regions of the nuclei. In several studies the sampling was from spherical busy cells in the rostral pole of the anteroventral CN, and this region is known to be responsive primarily to low frequencies.¹³⁴ Second, using the contralateral CN as a control may not be appropriate with evidence of strong commissural connections between cochlear nuclei.^{135–139} Stimulation of the ipsilateral CN by auditory nerve fibers undoubtedly produces activity in the contralateral CN via the commissural projections, thereby negating the idea that there is a simple dichotomy produced by the manipulation.

What emerges from these studies is the conclusion that congenital deafness, regardless of its cause, results in transneuronal changes that are expressed at the level of the CN. We shall now examine deafness-induced effects at higher centers of the auditory system. Ascending projections out of the CN exhibit abnormal pathways^{97,140–142} that impact on the structure of the target brainstem nuclei, including the superior olivary nuclei^{109,111,143} and inferior colliculus.^{144–147} These wide-ranging abnormalities are implicated as part of the explanation of why cochlear implants do not always produce beneficial outcomes.

◆ Higher Auditory Centers

The variable synaptic abnormalities within the CN in response to an SNHL, summarized in Fig. 3–5, may contribute to differential transmission delays along the central pathways, leading to corrupted temporal processing of auditory information initiated by cochlear implants. Changes within the CN could obviously have widespread effects because this structure serves as the gateway to the central auditory system. As one ascends the auditory pathway, it seems that transneuronal changes can occur at all levels.

Deafness and the Superior Olivary Complex

The deleterious effects of deafness evident within the CN, are also seen in more central structures. In the DWC, microscopic analysis of the lateral and medial superior olive and the medial nucleus of the trapezoid body demonstrated that neural soma and nuclei areas were 33 to 50% smaller in deaf compared with hearing cats.¹⁰⁹ The size of cerebellar Purkinje cells was not affected by an SNHL. There was also a 35% decrease in the number of synapses per unit somatic length in these nuclei in DWCs.¹¹¹ Analysis of the medial superior olive from deaf humans suggests a 20 to 30% reduction in neural soma area for the denervated structure.⁸⁸

Deafness and the Inferior Colliculus

In the midbrain, the central nucleus of the inferior colliculus (ICC) represents a key structure in the central auditory pathway. It is tonotopically organized and receives strong excitatory input from the contralateral ear, although most ICC neurons are binaurally influenced. Inputs to the ICC arise bilaterally from the superior olivary complex via the lateral lemniscus (decussating fibers represent the major pathway) and contralaterally from the dorsal and ventral cochlear nuclei.^{148,149}

Following a SNHL, significant structural abnormalities are observed in unilaterally deaf young animals when compared with both normal hearing and bilaterally deafened animals. Such studies revealed an increase in the afferent projection from the normal CN to the ipsilateral ICC.^{140,141,150} In contrast, bilaterally deaf animals show symmetry of the ascending projection that is similar to that in normal hearing animals.^{112,151} It would appear that these changes are driven by asymmetrical input to the central auditory system as a result of unilateral deafness. It is worth noting that the great majority of cochlear implant subjects also receive a strongly asymmetrical input via a single cochlear implant.

No difference was found between hearing and unilaterally deaf animals when studying ICC ultrastructure after 1 year of chemically induced deafness, although in bilaterally deaf cats, there was a reduction in the number of synapses compared with partial hearing or normal hearing cats.¹⁴⁴ A small but statistically significant reduction in neuronal soma area may be present in bilaterally but not unilaterally deaf cats.¹⁴⁶

Anatomic Changes Due to Electrical Stimulation

In patients who had some exposure to electrical stimulation via a cochlear implant, the range of neuronal soma size in the ICC was found to be as much as 30% smaller than normal.⁸⁸ Small study size, sampling bias, and laterality of stimulation may have obscured trophic effects if they were present, because all cell area averages were smaller than normal hearing controls. Cell soma area was smaller in cases of cochlear pathology than in cases of auditory nerve sectioning. This finding was postulated to be due to a dystrophic effect on neurons from a diseased cochlea, rather than the loss of trophic activity. This inference may have implications for models of deafness based on cochlear abnormalities.

Alternatively, neuronal soma size may not be a relevant (or is at best a crude) parameter in evaluating CNS changes due to deafness and electrical stimulation.

Metabolic Changes Due to Electrical Stimulation

Metabolic markers such as 2-deoxyglucose (2-DG) have been used to study the extent of neural activation in the ICC in response to electrical stimulation of the auditory nerve. Brown et al¹⁵² compared the effects of electrical versus auditory stimulation on 2-DG uptake in cats. Using acute, unilaterally deafened animals, the 2-DG uptake that was evoked from the deafened, electrically stimulated cochlea resembled that seen in the acoustically stimulated contralateral ICC. The location and extent of 2-DG uptake was dependent on the electrode configuration, electrode location, and stimulus intensity, although any increase in 2-DG uptake may also reflect an additive component arising from the ipsilateral auditory stimulation. In a different set of experiments, bilaterally deafened guinea pigs did not exhibit significantly reduced 2-DG activity in the ICC, and remained responsive to acute electrical stimulation after 15 months of deafness.¹⁵³ Schwartz et al¹⁵⁴ similarly observed normal 2-DG uptake in electrically stimulated deaf guinea pigs. The 2-DG labeling equaled but did not surpass levels observed in acoustically stimulated normal hearing controls. This effect was seen at increasing levels of stimulation, and with chronic stimulation. Collectively these studies suggest that in the unstimulated state, basic pathways for auditory information to the ICC in deafened animals remain largely functionally and structurally intact, indicating a powerful role for genetic programming of auditory connections.

Physiologic Changes Due to Electrical Stimulation

Frequency Representation in the Inferior Colliculus

Single cell activity evoked by electrical stimulation of the auditory nerve in neonatally deafened cats has revealed that major physiologic features of the ICC are preserved over wide durations of deafness.¹⁴⁵ The spatial tuning of the ICC studied in these acutely stimulated cats revealed that long-term deafness reduced the distance between basal and apical electrode neural representation in the ICC compared with that seen in cats with more auditory experience.

Experiments using neonatally deafened, chronically electrically stimulated cats have also been performed. Snyder et al¹⁵⁵ observed an increase in the ICC neural representation of the electrically stimulated sectors of auditory nerve. Correlating ICC recording depth with neural activity demonstrated a significant increase in neural representation of that sector of auditory nerve subject to chronic stimulation. Moreover, chronic electrical stimulation of the auditory nerve can induce a similar degree of plastic expansion in the ICC of adult-deafened implanted cats.¹⁵⁶ More recently, ICC recordings using multielectrode arrays have been

implemented.¹⁵⁷ When applied chronically, this technique promises to provide a longitudinal view of neural activity across the ICC in response to cochlear implantation.

Alternating stimulation of separate areas of the auditory nerve may preserve, or perhaps even sharpen, ICC representation of those stimulated sectors of auditory nerve.¹⁵⁸ These studies indicate that even in prolonged early-onset deafness, basic cochleotopic and neural representation of electrical stimuli may be elicited in the ICC. This developmental feature, however, is clearly modifiable by sensory experience. Neural plasticity of the ICC seems to expand the neural representation of chronically stimulated sectors of auditory nerve, even when those sectors receive stimulation long after the onset of deafness.

Temporal Response Properties

The ability of neurons in the ICC to synchronize their spike discharges to an auditory stimulus is referred to as temporal response properties. These properties allow for the encoding of sound features for speech recognition and word discrimination. Properties such as latency, jitter, and spike rate have been studied. Data are collected by presenting different electrical stimuli to deaf implanted animals, and modifying the duration of deafness, the duration of electrical stimulation, or the stimulus characteristics. Evidence suggests that early-onset deafness followed by chronic electrical stimulation of the auditory nerve may enhance the capacity of the ICC to encode high pulse frequencies, beyond those seen in normal hearing animals.¹⁵⁹ In addition, there is a maximum electrical pulse rate that may be encoded by the ICC, findings that have implications for stimulus parameters in the application of cochlear implants.^{145,159} Neurons in the ICC also appear to have higher temporal resolution when stimulated using amplitude-modulated electrical pulses compared with unmodulated stimuli.¹⁶⁰ Most ICC neurons are able to encode frequency-modulated stimuli up to 40 Hz. The carrier pulse rate eliciting response of neurons in the ICC was 104 pulses per second in unmodulated stimuli. By amplitude-modulating the stimuli, carrier pulse rate could exceed 600 pulses per second. Distortion of the neural response was observed as the ratio of modulation to carrier rate approached one fourth to one sixth. This observation may be significant, because cochlear implants can exceed these parameters. Following chronic stimulation at high rates, the ICC seems able to increase its average maximum following-frequency.¹⁶¹ High stimulation rates do not appear to impact the peak maximum following-frequency.

Increased latency and jitter of single unit responses were seen in long-term deaf, acutely stimulated cats.¹⁴⁵ Elevated stimulus levels ameliorated these changes. Significantly, chronically stimulating deaf cats at high rates reduced the median latency below that seen in normal-hearing cats.¹⁶¹ Overall, the ICC appears to retain the basic neural properties exhibited by normal-hearing animals. Chronic electrical stimulation may increase the temporal resolving capacity of the ICC, but the significance of this observation remains unknown.

◆ The Auditory Cortex

In 1942 Woolsey and Walzl¹⁶² reported the first cortical responses to electrical stimulation of the auditory nerve in normal-hearing cats. Subsequently, the primary auditory cortex (AI) in the normal-hearing animal was shown to be cochleotopically organized, and individual neurons within layer III/IV have well-characterized input-output functions for electrical stimulation and decreasing response latencies (to a minimum around 8 milliseconds) with increasing stimulus strength.^{163–166}

The changes in the auditory cortex after a SNHL are dependent on many factors, including the severity of the SNHL, whether the SNHL is unilateral or bilateral, and the developmental stage at the time of the SNHL. A further complication in the interpretation of changes in the auditory cortex in response to a SNHL, is that many “downstream” changes occur as a result of the SNHL (see previous sections), which effect the input, and the organization of that input, into the auditory cortex. At least some of the changes that occur in the auditory cortex as a result of a SNHL are plastic, and the return of input to the auditory cortex, via electrical stimulation of the auditory nerve, results in the reorganization of the auditory cortex. It is the plastic nature of the auditory cortex that is likely to be an underlying factor in the continued improvement in performance of cochlear implant patients with device use.¹⁶⁷

Morphological Changes Following Deafness

In contrast to the lower auditory centers, there is a scarcity of data on the morphologic changes that occur in the auditory cortex as a result of a long-term SNHL.¹⁶⁸ Nonetheless, reports of research in rabbits that were unilaterally deafened as neonates indicate that there is no change in neuron soma area, number of dendritic branches, or total basal dendritic length.¹⁶⁹ However, there is an apparent reduction in the number of spines along basal dendrites of lamina III/IV pyramidal neurons of the auditory cortex,¹⁷⁰ and a reorganization of “spine-free” but not “spiny” dendrites, with an increase in “nonspiny” dendrite length mostly in a tangential direction.¹⁷¹ In combination, these results indicate a loss of synapses within the auditory cortex after a prolonged deprivation of auditory input during development.

Although there have been reports that after pure tone stimulation the location of c-FOS-positive neurons within the auditory cortex (c-FOS is a protein associated with learning¹⁷²) matched the expected tonotopic organization,¹⁷³ there have been no reports of the effects of SNHL on either its localization or expression.

Physiologic Changes Following Deafness

The motto “use it or lose it” is often apt for cortical centers, and so reports of the activation of the auditory cortex by other modalities after an early SNHL are not surprising.^{174–176} However, as is the case for the ICC, there is evidence of the development of a “rudimentary cochleotopic representation” within AI, even when completely deprived of input.^{168,177} Other “higher-order” cortical auditory centers, including the secondary auditory cortex, on the

other hand, appear to be more susceptible to “infiltration” from other modalities and exhibit more plasticity than AI in the cat.^{178,179}

Field potentials and single- and multiunit recordings from layers III/IV of the auditory cortex in the DWC have shown that not only is a rudimentary cochleotopic representation present, but basic response properties, including growth functions and latencies, were similar to those in normal-hearing cats.¹⁷⁷ Corroborating results have been reported for short-term neonatally deafened cats,¹⁸⁰ although the cochleotopic organization was less robust, particularly in the dorsal part of AI, and became further degraded throughout the entire AI with extended periods of deafness.

Clearly, the AI does not develop entirely normally in the absence of sensory input; in fact there are different changes in the development of different layers within AI. Although the DWC develops a rudimentary cochleotopic representation in layers III/IV, there is a decrease in current sinks (and, therefore, presumably synaptic currents) at long (>30 milliseconds) latencies in layers II, III, and IV.¹⁸¹ The decrease in current sinks is even more evident in the deeper (infragranular) layers IV, V, and VI, and in these deeper layers the decrease is evident at all latencies. The infragranular layers are considered to be the output layers of AI, and therefore, in the DWC “efferent projections of the primary auditory cortex to sub-cortical structures and possibly also to higher-order cortical areas are probably substantially diminished.”¹⁸²

The effects of a restricted unilateral SNHL in adult animals, resulting from a cochlea lesion, and subsequent exposure to at least some auditory input, rather than a complete bilateral SNHL, are apparent in the reorganization of the contralateral AI. Under such conditions, the normal cochleotopic organization of the contralateral AI is distorted, and acoustic frequencies that correspond to regions of cochlea near the lesion-edge become grossly overrepresented.^{183–186} A unilateral SNHL not only affects the contralateral AI, but also results in the ipsilateral AI becoming more sensitive.^{185,187–189} Such reorganization could be due to “rapid disinhibition or true plastic reorganization with morphological changes,”¹⁸² and a contribution from the reorganization of interhemispheric corticocortical projections cannot be excluded.

Many of the studies of SNHL-induced changes in the auditory cortex utilize congenitally or neonatally deafened animal models, which allow access to the early critical period in development. However, changes in the response of neurons within the auditory cortex to a SNHL are not limited to this critical period, but can occur later in development.¹⁸⁹ There is a growing body of work supporting the plasticity of the adult auditory cortex, including AI.^{190–192}

Response to Chronic Electrical Stimulation

Chronic, behaviorally relevant, intracochlear electrical stimulation results in plastic changes in the deaf auditory cortex. Compared with unstimulated deaf controls, cats subjected to chronic electrical stimulation exhibit an increase in long-latency (>150 milliseconds) field potentials, larger current source densities (particularly in layers II and III)

and more sustained single- and multiunit activity.¹⁹³ There is also an expansion in the area of cortex activated by the electrical stimulation of the auditory nerve.¹⁹³ The resulting response properties of AI in chronically stimulated deaf cats are similar to those reported in normal-hearing animals. The long-latency responses are thought to be mediated by corticothalamic loops, and are proposed to be essential for short-term memory and processing in higher-order auditory centers.¹⁸² Therefore, behaviorally relevant, chronic intracochlear electrical stimulation appears to allow the auditory cortex to achieve an experience-dependent maturation, albeit not precisely as it would have occurred in the absence of a SNHL.

Clinical Changes Following Deafness

Many of the reports of changes in the auditory cortex in deaf patients, as in the animal studies of the cortex, have been focused on the “use it or lose it” scenario.¹⁹⁴ Therefore, it comes as no surprise that it has been reported that in prelingual deaf patients “the brain region usually reserved for hearing may be activated by other sensory modalities.”¹⁹⁵ However, the auditory deprivation-induced “takeover” of auditory areas appears to be limited to secondary auditory areas (supratemporal gyrus/perisylvian region), which are normally used for auditory processing and language.^{195–197}

Consistent with results reported from the animal models, the connections to AI appear to be more robustly organized than those to the secondary auditory areas, as there is no evidence of cross-modal activation of AI using either positron emission tomography (PET)¹⁹⁸ or functional magnetic resonance imaging (fMRI).¹⁹⁹ Auditory evoked potentials recorded from both cochlear implant and normal hearing subjects also suggest near-normal maturation of middle (IV and deep III) cortical layers. However, there appears to be altered maturation or input to the superficial (II, upper III) layers,²⁰⁰ particularly in the absence of auditory input during the early critical period.^{201,202} Therefore, as in the animal models, it appears that the auditory cortex, and in particular AI, remains in an immature state in prelingual deaf patients.²⁰³

Ipsilateral-contralateral differences in the responses of the auditory cortex in unilaterally deaf subjects are smaller than in normal-hearing subjects [magnetoencephalogram (MEG)^{204–207} and fMRI²⁰⁸]. The ipsilateral-contralateral changes can also occur in adult subjects as a result of a late-onset unilateral hearing loss,²⁰⁹ again highlighting the plasticity of the auditory system in the adult brain. Some changes may manifest within weeks of the hearing loss,²¹⁰ but changes continue to occur over a prolonged time course of 2 years or more,²⁰⁹ suggesting there may be both an unmasking of ordinarily silent inputs and morphologic changes. Interestingly, changes in the response of the ipsilateral auditory cortex may also be dependent on which side the unilateral deafness occurred,²¹¹ indicating that these changes may be at least partially a result of changes peripheral to the auditory cortex. These results emphasize the difficulties in determining if functional changes in the response of the auditory cortex are the result of changes within the cortex itself, or a result of downstream changes.

Despite many years of auditory deprivation, during which very low levels of activity are evident in AI, its activation can be seen using a variety of imaging techniques after the return of auditory input via a cochlear implant.^{212–215} In fact, after long-term cochlear implant use, auditory evoked potentials recorded from prelingual deaf patients, implanted in early childhood, appear nearly normal, suggesting an activation-induced maturation of the auditory cortex.²¹⁶ There are also plastic changes within the “higher-order” auditory centers, with the amount of activity in these centers in prelingual deaf patients with a cochlear implant decreasing with experience in using the implant.²¹⁷ There also is less activity seen in the higher-order auditory centers in prelingual deaf cochlear implant patients than in postlingual deaf cochlear implant patients.²¹⁸ Finally, long-term cochlear implant use also appears to enhance “top-down” feedback modulation of processing within lower auditory centers.¹⁹⁴

A final interesting observation is that there is a positive correlation between speech perception and low resting activity in AI prior to cochlear implantation for the prelingual deaf.²¹⁷ This relationship suggests that although AI and other higher-order auditory centers are capable of plastic change, as evident in the continued improvement in auditory performance with increasing experience using a cochlear implant,¹⁶⁷ the best clinical outcomes for cochlear implant patients may in fact occur with the most immature auditory cortex, or the “cleanest sheet.”

◆ Conclusions

Auditory experience plays a key role in laying down the fine organizational structure of the auditory pathway onto a framework generated by genetic cues. A lack of auditory experience during development results in a more rudimentary pathway; however, this reduced level of organization appears sufficient to provide both the temporal and spatial cues necessary for speech perception using a cochlear implant. Importantly, the ability of this pathway to undergo plastic reorganization following cochlear implantation is now recognized as a major factor underlying the clinical success of these devices. This chapter reviewed the degenerative and atrophic changes that occur within the auditory pathway following a SNHL and the trophic and functional reorganization that occurs following reafferentation via a cochlear implant.

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