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Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

An important goal of this Contract research is to examine the anatomical and functional consequences of patterned electrical stimulation delivered by a cochlear implant in the deafened developing auditory system. This Quarterly Progress Report presents a review paper summarizing our recent experimental findings and discussing their relevance to the clinical application of pediatric cochlear implants. First, we compare the efficacy of different stimulation modes and signals in inducing neurotrophic effects on cochlear spiral ganglion neurons (SG) in experimental animals that are deafened neonatally. Data suggest that: 1) intracochlear bipolar stimulation results in greater increases in SG survival than does extracochlear monopolar stimulation; 2) higher frequency, temporally challenging stimulation is more effective than low frequency (30 PPS) signals in inducing neurotrophic effects; 3) duration of stimulation plays an important role in the extent of neurotrophic effect seen; 4) implant insertion trauma offsets the neurotrophic effects of stimulation and results in regional SG cell loss that is proportionate to the degree of damage. Results from studies of the cochlear nucleus (CN) in these animals show profound effects of neonatal hearing loss on the volume of the CN (20% decrease) and on the cross-sectional area of large spherical cells in the rostral AVCN. Chronic electrical stimulation did not prevent or reverse this shrinkage in CN volume. However, spherical cell areas showed a modest but significant difference, with the stimulated CN cells showing a mean cell area (74% of normal) larger than that observed on the unstimulated side (68%).

The functional consequences of stimulation have been examined in electrophysiological recording experiments conducted in the inferior colliculus (IC). Results demonstrate that the orderly cochleotopic organization of the central nucleus of the IC develops normally in neonatally deafened cats and is unaltered by the lack of normal acoustic input during development. However, chronic electrical stimulation of a single bipolar or monopolar channel of a cochlear implant in these neonatally deafened animals induces: 1) significant expansion of the central representation of the stimulated cochlear sector and degradation of the cochleotopic organization of the IC, decreasing its frequency resolution; 2) a significant increase in the temporal resolution of IC neurons. Finally, some of the implications of these results with regard to developmental plasticity, critical periods and the clinical application of pediatric cochlear implants are discussed.

LONG-TERM EFFECTS OF DEAFNESS AND CHRONIC ELECTRICAL STIMULATION OF THE COCHLEA

Introduction

With the number of very young children now receiving cochlear implants, we believe it is important to determine the consequences of implantation and stimulation with the highly abnormal input delivered by a cochlear implant upon the deafened, developing auditory system. There have been few anatomical and physiological studies of the consequences of chronic electrical stimulation, and most of these studies have been conducted in adult animals. Published reports on the anatomical effects of cochlear implantation have focused primarily on issues of safety and damage (see Leake et al., 1990 for review). More recent work from several laboratories, however, has indicated that electrical stimulation of the cochlea can partially prevent the degeneration of the spiral ganglion neurons which otherwise occurs after deafness (Leake et al., 1991; Leake et al., 1992; Hartshorn et al., 1991; Miller et al., 1996). Our studies have been conducted in cats that are neonatally deafened by administration of the ototoxic drug, neomycin sulfate (60 mg kg I.M.), injected daily for the first 16 to 21 days after birth. Since kittens are born deaf, these animals have no normal auditory experience and are profoundly deaf by the age when adult-like hearing sensitivity would normally develop (i.e., about 21 days postnatal), thus modeling congenital or early-acquired profound hearing loss (Leake et al., 1997). The deafened animals are implanted unilaterally at the time of weaning, and the electrical signals delivered by the implant provide the initial and sole input to the developing auditory system. In this chapter, we will summarize results of research on the morphological and physiological consequences of chronic electrical stimulation in these neonatally deafened animals and discuss some of the implications relevant to pediatric cochlear implants.

Morphological Effects of Chronic Electrical Stimulation

Neurotrophic effects on cochlear spiral ganglion neurons.

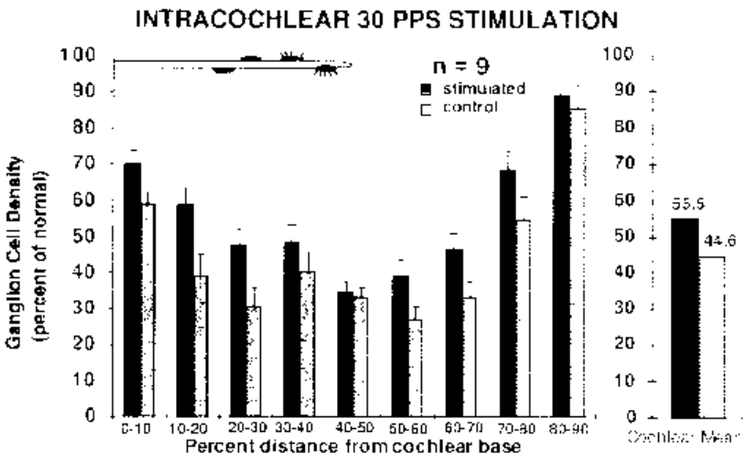
In kittens that are neonatally deafened by ototoxic drug administration, the cochlear pathology and degeneration of spiral ganglion neurons are progressive over time. Although there is substantial variation among animals in the extent of ototoxic drug damage, the cochlear pathology is very symmetrical between the two ears of each individual (Leake et al., 1991, 1992, 1995). This provides an excellent model for studying the effects of unilateral implantation and stimulation, using paired comparisons with the contralateral cochlea of each animal serving as its own control.

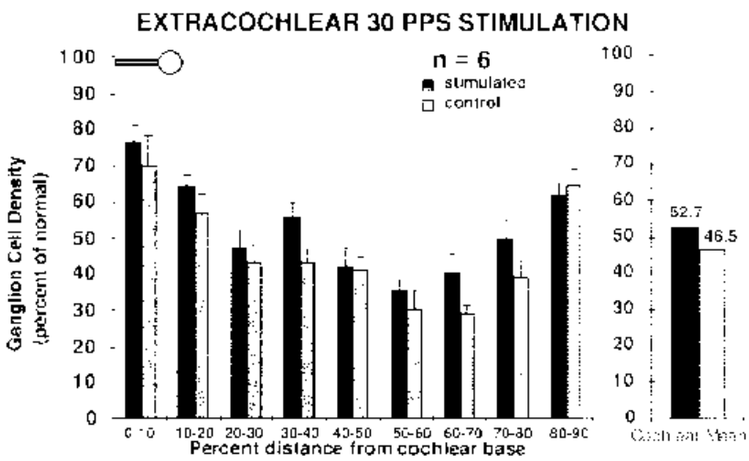
Hearing losses are assessed by auditory brainstem response (ABR) testing at the end of ototoxic drug treatment and again at the time of implantation. All subjects included in these studies have profound hearing losses, with no ABR response to clicks and no frequency following response to 500 Hz tones at 110 dB peak SPL. Bipolar scala tympani electrodes are implanted unilaterally in the deafened animals at the time of weaning, at about 6-8 weeks of age. In initial chronic stimulation studies, the electrical stimuli were simple, charge-balanced pulses (200 μsec phase)

delivered continuously at a rate of 30 pps. Stimulus intensity was set at either 2 or 6 dB above individual EABR threshold, and animals received stimulation for 4 hours per day, 5 days a week over periods ranging from 13-23 weeks (mean duration = 15.7 weeks). Paired comparisons between the stimulated ears and the contralateral deafened cochleas demonstrated higher spiral ganglion cell density on the stimulated side (Leake et al., '91,'92), with a mean overall increase of about 17% of normal density that was highly significant in a group of 9 animals (Figure 1a).

Since electrical stimulation can help maintain the auditory neurons, it has been suggested that it might be advantageous to implant a less invasive, ball-type round window electrode and use monopolar stimulation in a young deaf child to maintain the auditory system for later implantation of a multichannel cochlear implant. This would lessen some of the problems encountered with implanting very young children, such as increased incidence of device breakage (due to falls, etc.) and difficulties in appropriately adjusting processors. In addition, the effects of the broad band stimulation delivered by this type of electrode are of interest from the standpoint of understanding the limits of developmental plasticity in the auditory system, since research on other sensory systems has shown that such widely distributed synchronized activity can exert a powerful organizing influence in the developing nervous system (See Discussion). To address these questions directly, the consequences of stimulation with a monopolar round window electrode were examined in separate experiments (Leake et al., 1995). Neonatally deafened kittens were implanted at 6-8 weeks of age with electrodes positioned on or just inside the round window and again were stimulated with charge-balanced pulses (30 pps; 4 hours a day; 5 days per week) for 12-28 weeks (mean duration = 22 weeks). As suggested by van den Honert and Stypulkowski (1987) and as demonstrated in final electrophysiological experiments in these animals, such electrodes activate neurons with a very broad distribution (wide range of frequencies) in the auditory nerve array at the current levels employed for chronic stimulation (6 dB above EABR threshold). Given this broad activation of the nerve, and because stimulation was initiated at a younger age and there was no damage from insertion of a long scala tympani electrode, we hypothesized that the "protective effect" of electrical stimulation in preventing ganglion degeneration would be maximized. Instead, as illustrated in Figure 1b a much more modest (although still significant: $P<0.01$, Student's pair t test) increase in spiral ganglion density, only about 6% overall, was observed in this group (Leake et al., 1995).

This extracochlear study and the earlier intracochlear experiments were conducted using simple 30 pps pulse trains for chronic stimulation. Recently, additional experiments have been conducted using selected higher frequency signals, including: a) 80 pps unmodulated pulse trains, b) stimulation delivered by a single channel processor transducing environmental sounds into an electrical analogue signal, or c) 300 pps pulse trains that were sinusoidally amplitude modulated (modulation depth, 100%) at 30 Hz. Spiral ganglion density data from this group showed more pronounced trophic effects on neural survival. Mean increases of more than 35% were seen in some cochlear regions, and an overall increase of more than 21% of the normal cell density was observed in the stimulated cochleas above that in the control deafened cochleas (Fig. 1c; Fig. 2).





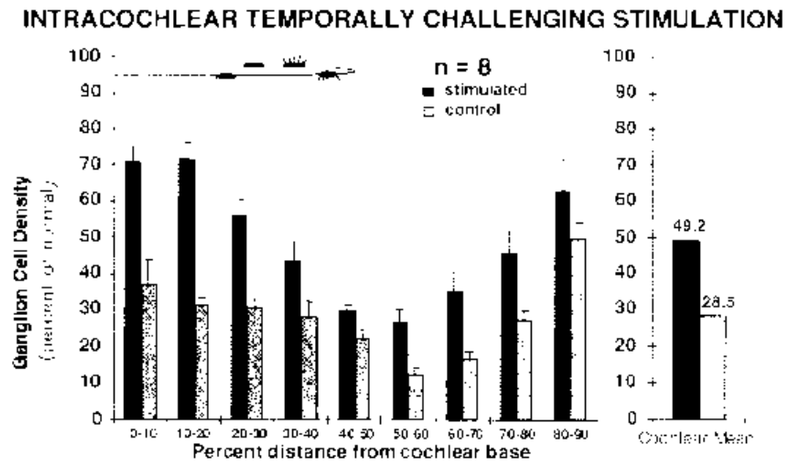


Figure 1. Spiral ganglion (SG) cell density (volume ratio) in the implanted, chronically stimulated cochleas (black bars) as compared to the contralateral deafened, unstimulated cochleas (shaded bars) in three different groups of neonatally deafened cats. Data are shown as percent of normal for 10% sectors of the cochlea (base to apex). **a.** In the intracochlear 30 pps stimulation group the overall average cell density in the stimulated ears was 21% higher than in the control ears. Note that clear increases in SG are seen throughout the cochlea with the exception of the 40-50% region where the tip of the electrode caused insertion trauma. **b.** In the extracochlear 30 pps monopolar stimulation group the overall increase in neural survival was only 6%. **c.** The temporally challenging intracochlear stimulation group showed the greatest trophic effect with an increase of 72%, but stimulation periods were also longer in these subjects allowing time for further degeneration on the contralateral side. Note that marked increases in survival are seen in all sectors of the cochlea except in the 40-50% region where the difference is very modest because insertion trauma at the tip of the electrode array in all of the implanted cochleas resulted in decreased cell survival here.

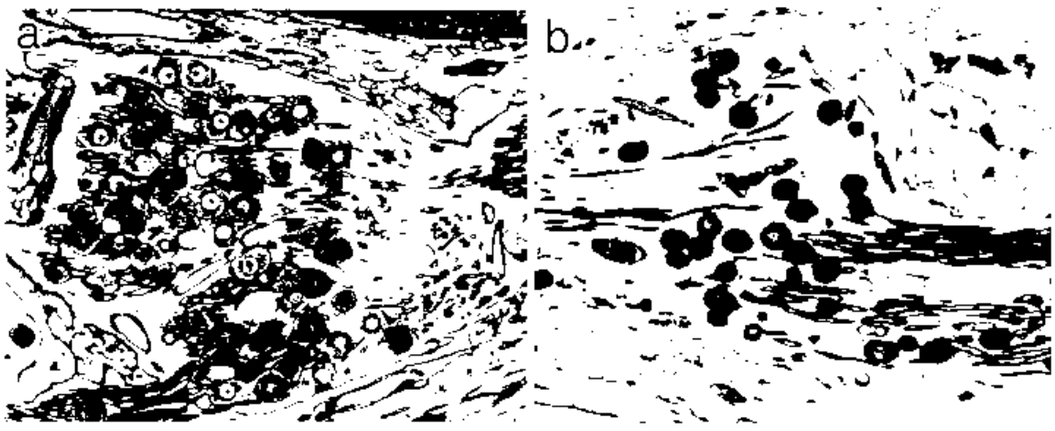


Figure 2. Histological sections illustrating the spiral ganglion cells in the basal turn of an animal in the temporally challenging stimulation group. The section in (a) was taken from the stimulated cochlea and (b) shows the same region from the contralateral deafened unstimulated ear. Sections are representative of the cochlear region 20-30% from the base, where these cells showed a marked difference in neural survival, with ganglion cell density at 85% of normal in the stimulated cochlea and 44% of normal on the opposite unstimulated deafened side.

It should be noted that if these data from the temporally challenging stimulation group are expressed as *percentage increase* (instead of percent of normal differences), the stimulated cochleas (at 49.2% of normal) show more than *70% increase* over the unstimulated cochleas (28.5%).

In addition to the increased density of spiral ganglion cells in the stimulated cochleas, electron microscopy shows that the remaining cells have more normal morphology. Many of the cells maintain myelination of the cell soma (figure 3a), in contrast to the control deafened unstimulated cochleas in which most of the cells have become demyelinated (figure 3b) after prolonged deafness.

The degree to which this enhanced maintenance of the spiral ganglion neurons relates to the specific electrical signals employed as opposed to the longer duration of stimulation (21-44 weeks) is not clear. However, in comparison to the earlier intracochlear and extracochlear studies, these data provide a marked contrast. From these results we conclude that the effect of electrical stimulation in preventing degeneration of the auditory nerve is highly significant over prolonged periods of stimulation, and that the specific parameters (electrical stimuli, duration of stimulation; and mode of stimulation (e.g., extra- vs. intracochlear) may be critically important in maximizing this protective effect.

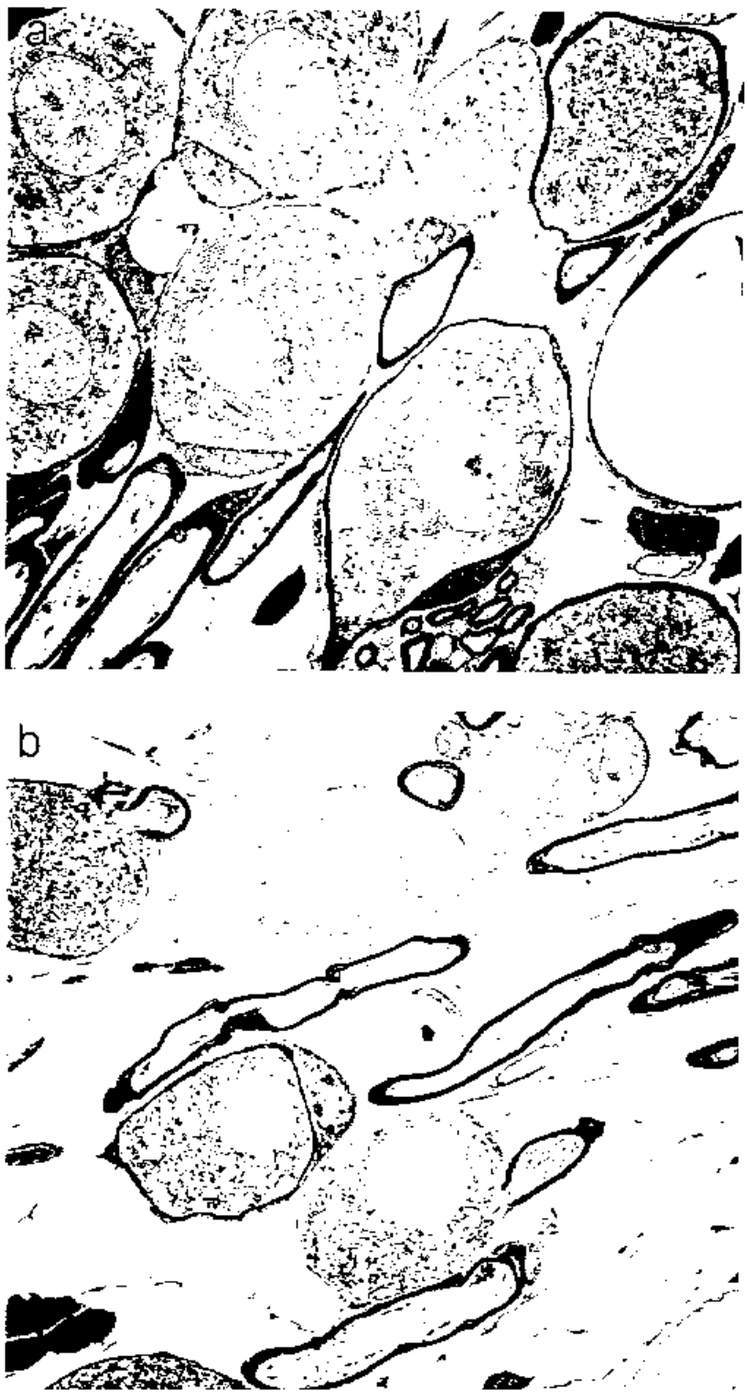


Figure 3. Electron microscopy of the spiral ganglion cells taken from the same cochleas illustrated in Figure 2. The cells in the stimulated cochlea (a) show more normal ultrastructural morphology with higher density of cells and many of the cell somata maintaining normal myelination as compared to the cells in the same region of the contralateral deafened control cochlea (b).

In these recent experiments, chronic electrical stimulation was applied at relatively low current levels, set at just 2 dB above the evoked response threshold as determined for each individual subject. When final electrophysiology experiments were conducted in these animals, data suggest that the chronically applied stimuli excite fibers over a more limited distribution within the cochlear than that over which ganglion cell conservation was seen. For example, activation of a given bipolar electrode pair at 2 dB above EABR threshold might be estimated to excite about one-third of the auditory nerve array, while chronic stimulation at that level in the same cat resulted in significant ganglion cell conservation throughout the entire cochlea. Furthermore, the extent of maintenance of spiral ganglion cells was not altered significantly by reducing the chronic stimulation level from 6 dB to 2 dB re: EABR threshold (Leake et al., 1992), and as discussed previously, maintenance was actually decreased with extracochlear stimulation which activates a very broad distribution of auditory neurons. These observations suggest that *direct activation of spiral ganglion cells may not be the direct (or only) cause of ganglion cell maintenance.* A number of different mechanisms must be considered as possible contributors to this effect, such as reflexive vascular changes (e.g., mediated by sympathetic innervation), chronic activation of the efferent system, upregulation of neurotrophic agents, subthreshold trophic influences of electrical fields, etc. It is important to resolve these questions because understanding of the direct cause(s) of spiral ganglion maintenance will almost certainly provide insights into how stimulation with a practical device in a young child might result in optimum preservation of the auditory system.

Cochlear implant insertion trauma.

An additional important result from these morphological studies is the consistent finding that insertion trauma induced by implantation of intracochlear electrodes, even slight damage to the osseous spiral lamina or basilar membrane, markedly decreases ganglion cell survival. The tip of our cat electrode frequently caused insertion trauma in the cochlear region 40-50% from the base in most of the implanted cochleas in these studies. The trophic effects of stimulation in maintaining higher neural survival were largely offset by the effects of the mechanical trauma in this cochlear region (see Figures 1a and c). Moreover, the degree of damage caused by the implanted electrode was clearly related to the extent of ganglion cell loss seen in histological sections (Figure 4). Recent studies using advanced imaging techniques (submillimeter computerized tomography) in human cochlear implant subjects have demonstrated great intersubject variation in the intracochlear positioning of implanted electrodes, and a high incidence (about one-third in a group of 30 subjects) of insertions that would produce mechanical trauma, including array compression, twisting and intrascalar excursions of electrodes (Ketten et al., 1998). Clearly, improved intracochlear electrodes that minimize the likelihood of such mispositioning, and the trauma and resulting spiral ganglion cell loss, should be a priority in the design of future generations of cochlear implants.

Figure 4. Histological sections illustrating the insertion trauma caused by the tip of the electrode array in the implanted cochleae in two subjects from the temporally challenging stimulation group. Such mechanical damage consistently resulted in reduction in spiral ganglion cell density. The micrograph in (**a**) is taken from the same case as shown in Figure 2 which showed such marked trophic effect of stimulation in the 20-30° sector. In the 40-50° region shown here the tip of the implant caused minor mechanical damage, resulting in dislocation of the basilar membrane attachment to the spiral ligament (arrows) and very slight displacement of the outer edge of the osseous spiral lamina (arrowheads). Even this slight damage offset the trophic effects of stimulation so that density of ganglion cells (G) was equal (≈33% of normal) in this region of both cochleas. The micrograph in (**b**) shows another example of insertion trauma which caused a small fracture of the osseous spiral lamina (arrow) extending over ≈ 1mm in the 40-50° region. Again, the increased survival of spiral ganglion cells (G) seen in other regions was offset by this damage and cell density was only ≈20% of normal.

Effects of Deafness and Chronic Electrical Stimulation on the Cochlear Nucleus

Histological studies of the cochlear nuclear complex of these neonatally deafened cats have demonstrated profound degenerative changes that are progressive for many months after deafening (Hultcrantz et al., 1991; Tustig et al., 1994). As compared to data from normal adult cats, the cochlear nuclei (CN) of deaf animals show: i) significant shrinkage in the total volume of the CN as compared to normal adults; ii) a striking reduction in the density (number of cells unit area) of spherical cells within the rostral anteroventral cochlear nucleus (AVCN); and iii) a significant reduction in the mean cross-sectional area of large spherical cells in the rostral AVCN. These results are consistent with many previous studies showing that neonatal sound deprivation or deafening causes profound adverse degenerative changes in the cochlear nuclei (Coleman and O'Connor, 1979; Coleman et al., 1982; Evans et al., 1983; Trune, 1982; Webster, 1988; Webster and Webster, 1977, 1979). Comparisons between the stimulated and control CN in the intracochlear, 30 pps stimulation group show no significant differences in either nuclear volume or spherical cell density after chronic stimulation. However, for the final histological measure, cross sectional area of the large spherical cells in the rostral AVCN, a modest but significant difference is demonstrated, with cells in the stimulated CN measuring 6% larger than cells in the contralateral deafened CN (Tustig, 1994). Interestingly, virtually identical results were seen in the CN after temporally challenging stimulation. As compared with data from normal adult cats these deaf animals show marked shrinkage in CN volume (about 20%), but no difference between stimulated and control sides (Figure 5a). Again, a significant but modest 6% increase in spherical cell area is induced by chronic stimulation (figure 5b) in these animals with >20% of normal increases in spiral ganglion cell density.

It is unclear why electrical stimulation is relatively ineffective in preventing or reversing the pronounced morphological changes in the CN after deafness, even though these same animals show marked increases in spiral ganglion survival induced by intracochlear electrical stimulation. One possible explanation may lie in the delay between deafening and implantation in these animals. Ototoxic drugs are administered neonatally, during the early period of rapid growth of the CN, but electrical stimulation is initiated after weaning, at about 8 weeks of age. It is possible that the electrical stimulation in these animals was too late in development to prevent the profound consequences of early deafness. It will be extremely interesting to see if CN stimulation-induced changes are greater in the recent high frequency stimulation group where such marked differences in spiral ganglion density are observed. Matsushima et al. (1991) conducted a similar study of 4 animals that were deafened at 1 month of age (rather than neonatally). They reported more pronounced effects of chronic electrical stimulation on both cell size and cell density in the CN. The difference in results between these two otherwise similar studies suggests that the age at time of deafening may be a critical parameter in determining whether the CN is sensitive to stimulation-induced "protective" effects.

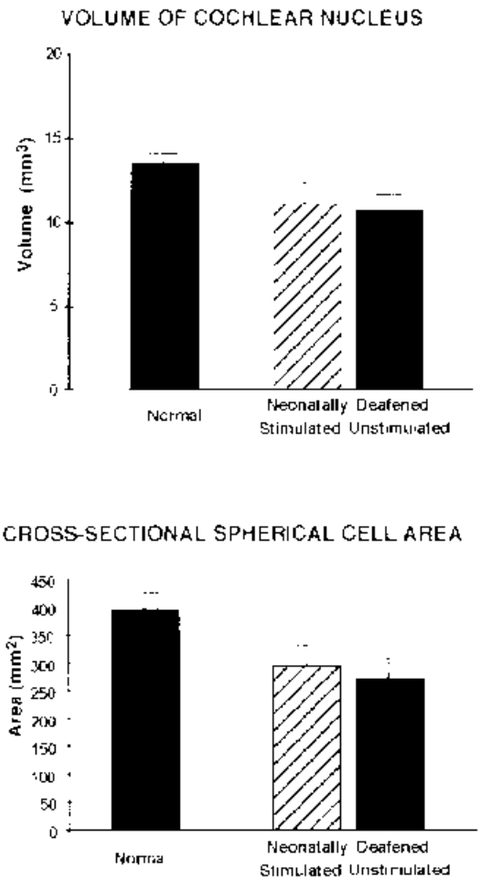


Figure 5. Data showing cochlear nucleus volume and cell size in normal cats and in 4 neonatally deafened animals from the recent high frequency stimulation group. **a.** The mean total volume of the cochlear nucleus was markedly reduced in the neonatally deafened animals, but there was no significant difference between stimulated and deafened control nuclei, despite the markedly increased survival of cochlear spiral ganglion neurons (mean increase of 21%) seen with chronic stimulation in these subjects. **b.** The cross-sectional area of spherical cells in the rostral AVCN was reduced to about 68% of normal after neonatal deafening in the unstimulated control ears. The AVCN on the chronically stimulated side showed a mean spherical cell area of 74% of normal, a 6% increase that was statistically significant in paired comparisons (student's *t* test, $p<0.01$).

Functional Consequences of Chronic Electrical Stimulation

Alterations in Spatial Selectivity (Cochleotopic Organization) in the Auditory Midbrain

Acute electrophysiological experiments have examined the topographic organization and the temporal patterns of neuronal responses evoked by cochlear electrical stimulation within the auditory midbrain (Snyder et al., 1990; Snyder et al., 1991, Snyder et al., 1995). Studies have been conducted in: i) "normal" animals that were deafened, implanted as adults and studied acutely; ii) neonatally deafened, chronically implanted but unstimulated controls; and iii) the 3 neonatally deafened, chronically stimulated groups (intracochlear 30 pps, round window monopolar 30 pps, and high frequency stimulation groups) described above. Data from these studies suggest that the selectivity of neural activity normally accounting for the frequency representation within the principal midbrain auditory nucleus, the central nucleus of the inferior colliculus (IC), develops normally (or nearly so) in neonatally deafened cats if they are not chronically stimulated. That is, the area within the IC activated by a single bipolar electrode pair (the spatial tuning curve or STC, measured at 6 dB above minimum threshold) in neonatally deafened, unstimulated animals is 0.8 mm. This is identical to the value measured in "normal" adult deafened cats (STC width = 0.8 mm). On the other hand, when these deaf animals are chronically stimulated at a young age, even at low stimulus intensities, spatial selectivity is markedly altered. The central representation of cochlear location is significantly expanded. The STCs of chronically activated electrodes, measured at 6 dB above minimum threshold, are about 1.5 times larger (STC width = 1.25 mm) than those of identical electrodes implanted in either control deaf littler mates, or in acutely deafened ("normal") adults (Figure 6).

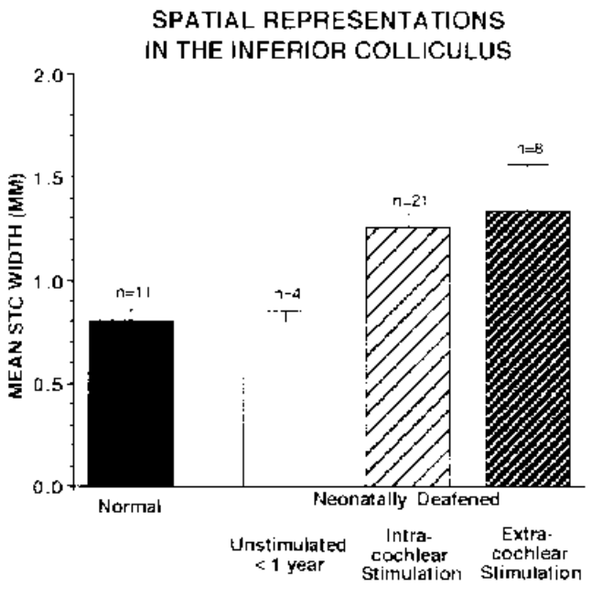


Figure 6. Data on selectivity of stimulation as indicated by electrical threshold functions or STCs, which indicate the area of the IC activated by a single bipolar electrode pair. The STC widths are measured at 6 dB above minimum threshold and averaged for each animal. In normal cats the average STC 6 dB width was 0.80 mm. Neonatally deafened, unstimulated cats were identical to the normals. The data for intracochlear stimulation include both the 30 pps intracochlear stimulation group (n=11) and the recently acquired data for the temporally challenging stimulation group (n=10) and show a highly significant increase in STC width to 1.25 mm. The extracochlear stimulation group show a similar increase in IC spatial representation with a mean STC width of 1.33, but the variance is great in this group as indicated by the bar showing standard error.

Our findings suggest that electrical stimulation using a single intracochlear bipolar pair can result in significant distortion of the cochleotopic organization of the central auditory system, at least to the level of the midbrain (Snyder et al., 1990, Leake and Snyder, 1994; Leake et al., 1995). This type of functional change can be interpreted as reflecting the developmental plasticity of the auditory system. The initially restricted area excited by the stimulated cochlear neurons expands over time as the brain adapts to and makes optimum use of the only available input. However, such massive expansion of the representation of one electrode pair, if irreversible due to critical period limitations, would clearly limit the possibilities for selective stimulation later with multiple electrodes. This may be a potential problem with implants in young children in whom "fitting" and setting channel loudness levels can be very difficult.

Results for IC data following extracochlear monopolar stimulation were similar to those from the intracochlear stimulation experiment, again showing markedly expanded spatial representations (STC width = 1.33). However, variability was much greater in the extracochlear group, suggesting that the functional consequences of such stimulation may be highly unpredictable. Nearly normal selectivity was seen in some animals, indicating that functional changes apparently do not always occur with this broad band stimulation. In contrast, striking increases in STC widths were observed in other animals, suggesting that under certain conditions extracochlear monopolar stimulation can induce profound and potentially deleterious functional alterations in the central nervous system (Leake et al., 1995). This finding of distortion of spatial representations in the IC and the finding that extracochlear stimulation is less effective than intracochlear stimulation in preventing the degeneration of auditory neurons both strongly argue against the use of such stimulation in a young child for the purpose of maintaining the auditory system for later application of a multichannel cochlear implant. However, because of the great variability in results with monopolar extracochlear stimulation, these data do not provide compelling evidence in regard to the initial hypothesis that this highly synchronized, electrical activation of broadly distributed auditory neurons would result in profound functional reorganization (similar, for example, to the consequences of stroboscopic illumination effects in the developing visual system; see Discussion).

Chronic Electrical Stimulation Alters Temporal Response Properties of IC Neurons

Additional electrophysiological studies in these neonatally deafened animals have analyzed temporal response properties of single neurons in the IC driven by electrical stimuli. Data have shown that many temporal features of IC unit responses to electrical stimuli are very similar to those seen with acoustic stimulation. In "normal" cats that are deafened and implanted as adults, all major IC response types can be identified, and first spike latencies as well as phase-locking capacities appear nearly identical to those observed with acoustic stimulation. However, quantitative analysis of response patterns (post-stimulus time histograms) in neonatally deafened cats that were chronically stimulated at a young age reveal several stimulus-induced alterations in temporal responses properties (Snyder et al., 1991). For example, in neurons of chronically

stimulated cats the occurrence of inhibitory and late responses is significantly increased. Further, a clear difference among experimental groups is seen in the temporal resolution of IC neurons (i.e., the ability of these neurons to follow pulse trains of increasing rates). Temporal resolution of neurons in the central nucleus of the IC is decreased by severe sensory deprivation during development after neonatal deafening, and is restored or increased by subsequent chronic electrical stimulation (Snyder et al., 1995). Quantitative analysis of frequency transfer functions for all IC neurons in adult deafened "normal" control animals, shows an average maximum following frequency of 104 pps (Figure 7, black data bar). Neonatally deafened, unstimulated animals demonstrate a decrease in the temporal resolution of IC neurons with an average maximum of 81 pps. In contrast, animals that are neonatally deafened and chronically stimulated with low frequency biphasic pulse trains (30 pps), show a restoration or maintenance of normal temporal resolution with a mean maximum following frequency of 107 pps (not significantly different from normal). Finally, experimental animals that are chronically stimulated with higher frequency, temporally complex (and in some animals behaviorally relevant) stimuli demonstrate a pronounced increase in temporal resolution with a mean maximum following frequency of 142 pps.

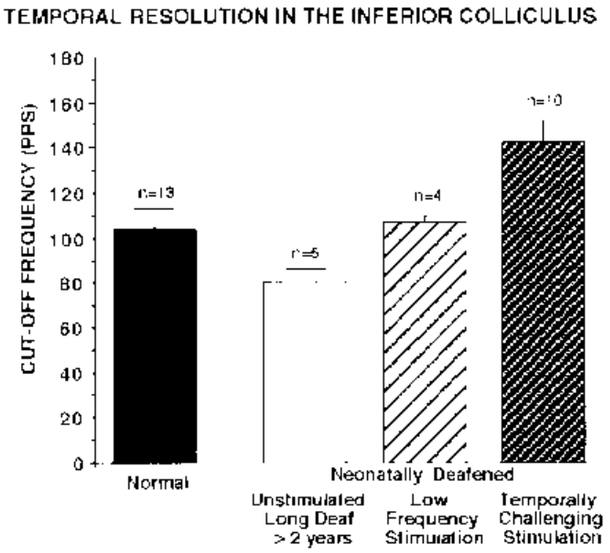


Figure 7. The mean maximum following frequency for neurons in the inferior colliculus in adult deafened "normal" cats (104 pps) is compared to 3 groups of neonatally deafened cats. Unstimulated, neonatally deafened cats studied after prolonged periods of deafness show a clear reduction in temporal resolution to a mean value of 81 pps. In contrast, neonatally deafened animals that were chronically stimulated at 30 pps exhibit maintenance or restoration of normal temporal resolution with a mean maximum cutoff frequency of 107 pps, and cats stimulated with higher frequency, temporally challenging signals show a pronounced increase in frequency following capacity to 142 pps.

These results suggest that the temporal resolution of the central auditory system in deaf animals can be profoundly altered by experience with electrical stimulation. Further, the magnitude of this effect on temporal resolution *depends upon the specific temporal properties of the electrical signals delivered to the cochlea.* These frequency-dependent effects of chronic stimulation in increasing the capacity of midbrain neurons to resolve relatively fast temporal events are potentially important in understanding differences between the auditory performance of human cochlear implant subjects and in understanding how subjects improve over time. We hypothesize that this ability to follow electrical pulse trains at higher frequencies may relate to the success of modern "CIS" speech processor designs which utilize amplitude modulation of high frequency pulse trains. Moreover, it is possible that the poorer speech recognition performance in some patients may be related to an inability of the central auditory system to entrain to higher frequencies (e.g., due to specific deafness pathologies).

Discussion: Developmental Plasticity and Critical Periods

It is unclear what role "critical periods" play in the effects of stimulation seen in our neonatally deafened cats. There is considerable evidence from research in other sensory systems that input activity, especially synchronized activity, exerts a powerful organizing influence on the developing nervous system. For example, the development of normally refined connections in the visual system can be prevented by introducing widely distributed, synchronous inputs to the retina, either by electrical stimulation of the optic nerve (Stryker and Strickland, 1984; Weliky and Katz, 1997) or by stroboscopic illumination that results in nearly synchronous inputs from both eyes (Cremieux et al., 1987; Eisele and Schmidt, 1988). Moreover, as is potentially relevant for these cochlear electrical stimulation experiments, segregation of inputs from the two eyes can be sharpened by exaggerating the temporal decorrelation of their inputs, for example by introducing a prism over one eye (Tumosa et al., 1980; Van Sluyters and Levitt, 1980) or by alternate monocular deprivation (Hubel and Wiesel, 1965; Tumosa et al., 1980; Altman et al., 1987). These results are interpreted as reflecting the effects of competitive processes which act to segregate different input populations driven by uncorrelated inputs.

Although there is a normal 'critical period' for these coincidence-based developmental effects in the visual system, this period is extended substantially in animals that are deprived of normal sensory inputs (e.g., see Cynader and Mitchell, 1980; Mower and Cristen, 1985). Once inputs are reintroduced, a critical period is initiated and results in reorganization that stabilizes over a period of 6 to 8 weeks in animal models. *If the central auditory system is governed by similar developmental mechanisms, then a period of chronic electrical stimulation with an implant during an extended postnatal period in a congenitally deaf child might be expected to generate parallel organizational changes. As in the visual system, this stimulation might initiate the onset of a delayed 'critical period,' which would render stimulus-induced changes irreversible.*

It is well-known that early sound exposure is important for development and maturation of the auditory pathways in mammals and that neonatal sound deprivation results in profound adverse

effects on the central auditory system (Eggermont and Bock, 1986; Rubel et al., 1984; Rubel et al., 1990; Rubens and Rapin, 1980). After neonatal deafening or conductive hearing loss, animals show pronounced atrophy of the cells in the cochlear nucleus (CN) (Coleman and O'Connor, 1979; Coleman et al., 1982; Trune, 1982; Webster and Webster, 1977, 1979), decrease in the volume of the CN (Coleman et al., 1982; Trune, 1982; Webster, 1988), physiological changes (e.g., Evans et al., 1983), as well as transneuronal changes at higher levels of the auditory system (Feng and Rogowski, 1980; Jean-Baptist and Morest, 1975; Powell and Erulkar, 1962). Other research has shown that neonatal cochlear lesions can result in dramatic modification in the anatomical projections from the contralateral CN to the superior olivary complex and inferior colliculus (Moore and Kitzes, 1985; Moore and Kowalchuk, 1988; Nordeen et al., 1983; Moore, 1994; Russell and Moore, 1995; Kitzes, 1996). Further, many studies suggest that deprivation later during development does not have the same profound impact on the central auditory system (Blatchley et al., 1983; Webster, 1983). Thus, auditory deprivation during early development clearly produces profound changes, and there is evidence for the existence of critical periods.

However, these studies have been conducted in a wide variety of species, and in many different models of deprivation and deafness. Thus, the specific nature and timing of critical periods and the role of early auditory deprivation for later structural and functional development of the central auditory system as would apply either in a young deaf child or in our pediatric deaf animal model are currently unknown. Our neonatally deafened kittens are deafened over the period when spontaneous activity would normally be developing in the auditory nerve and the organ of Corti and cochlear innervation patterns are undergoing dramatic maturation (Walsh and McGee, '86; Walsh and McGee '82; See Walsh and Romand, 1992 for review). Clearly, these animals undergo severe auditory deprivation and have no normal auditory experience to drive the development of central pathways and processing mechanisms. However, electrical stimulation is not initiated until kittens are weaned at about 6 weeks postnatal. Critical and or sensitive periods in normal auditory system development might be completed by this age, and whereas critical periods in visual system development are delayed by bilateral deprivation, such mechanisms have not yet been defined in auditory system development. We do not know, for example, whether the expanded spatial representations (increased STC widths) in the IC of our neonatally deafened cats reflect actual anatomical changes in the connectional selectivity of auditory pathways, nor is it known whether or not these changes are reversible. These are clearly important questions for future research.

Other laboratories studying the effects of electrical stimulation in adult deafened animals have reported conflicting results. Three studies in guinea pigs have suggested that chronic electrical stimulation can also induce protective effects on spiral ganglion neurons in animals that have matured normally and are deafened and stimulated as young adults (Lousteau, 1987; Hartshorn et al., 1991; Miller and Altschuler, 1995; Miller et al., 1996). However, other investigators, including Shepherd who studied kittens deafened at 1 month of age rather than neonatally (Shepherd et al., 1994) and Li, et al. who studied guinea pigs (Li, Webster and Parkins, 1997) have found *no*

evidence of a neurotrophic effect of electrical stimulation on spiral ganglion cell survival. Moreover, functional studies of the effects of chronic stimulation have not been reported in adult deafened animals. Given the paucity of data currently available, we believe it is premature to draw definite conclusions regarding the age-dependence of the various effects of chronic electrical stimulation.

Summary

In summary, our findings clearly demonstrate that chronic electrical stimulation of the cochlea results in significant conservation of the spiral ganglion neurons which otherwise progressively degenerate in neonatally deafened animals that model profound congenital or early-onset deafness. While it seems likely that optimized stimulation by an implant can result in parallel maintenance of auditory neurons in a child with early-onset deafness, an understanding of the fundamental mechanism(s) underlying this neural protection is critical to maximizing potential benefits. In addition, physiological studies have shown that there may be potential deleterious effects of chronic stimulation, as it can result in a substantially negative functional remodeling of cochleotopic representations in the auditory brain stem. Thus, a pediatric cochlear prosthesis must be optimized to conserve not only the spiral ganglion neurons, but also the topographic and temporal representations which underlie signal processing within the central auditory system. *The mode and nature of the electrical signals that are introduced through an implant in a young deaf child should be carefully considered as the critical initial input to a developing sensory system that is capable of substantial plastic remodeling.*

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Work planned for the next quarter

1) Two acute electrophysiology experiments are planned for the next quarter to study chronically stimulated cats. These subjects are neonatally deafened animals in GM1 ganglioside experiment that have received stimulation alternating between 2 bipolar intracochlear channels on the implant, using the "training" protocol consisting of weekly increments in pulse AM frequency (i.e., 1 week of stimulation at: 100 pps; 300pps 30Hz AM; 500pps 40 Hz AM; 800pps 50 Hz AM; then repeating the series.

2) Cochlear histopathology studies will continue with the evaluation of data from 2 animals in the GM1 ganglioside series: 1) a control animal sacrificed at the time its littermates underwent implant surgery and initiated chronic stimulation; and 2) the first animal in our 2-channel stimulation group that completed the stimulation using the new "training" protocol and was studied in a terminal electrophysiology experiment. Two additional animals in the GM1 series will continue chronic stimulation throughout the next quarter in addition to the 2 that will be studied in terminal experiments.

3) Several members of our group will attend and present data at the 1999 International Conference on Implantable Auditory Prostheses to be held at Asilomar Conference Center in Pacific Grove, CA, August 29 through September 3. Drs. Leake and Snyder are invited speakers; Stephen Rebscher, Charlotte Moore and Marcia Raggio will present posters.