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Protective and Plastic Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

Many morphological studies have shown that auditory deprivation, especially deprivation at an early age, results in progressive degeneration in both the auditory periphery and the central auditory system. However, relatively little is known about the functional consequences of long-term auditory deprivation or of chronic electrical stimulation initiated after prolonged durations of deafness on the processing of electrical signals in the central auditory system.

Recently, we reported data on temporal resolution of IC neurons in neonatally deafened animals, specifically focusing on subjects studied as adults after ***prolonged durations*** of deafness of ≥2.5 years (Vollmer et al., 2005). Cochlear pathology was very severe in these long-deafened animals, and the mean spiral ganglion cell density was less than 10 % of normal. When these animals were studied in acute terminal physiological experiments, they exhibited significantly degraded temporal following in the auditory midbrain, as indicated by the capacity of neurons in the IC to phase lock to trains of electrical pulses delivered at increasing pulse rates (Rebscher et al. 2001, Vollmer et al. 2000). We initially hypothesized that this functional limitation was due to the severe cochlear pathology and therefore would be irreversible when a second group of these long-deafened cats received a cochlear implant and chronic electrical stimulation. Surprisingly, however, after several weeks (mean 21.4 wks) of experience with stimulation delivered by a cochlear implant, long deafened subjects showed a significant increase in the temporal following capacity of IC neurons and concomitant decreases in first spike latencies (Vollmer et al., 2005). In fact, temporal following was increased not just to a level equivalent to normal controls but significantly higher, and equal to the increases demonstrated in cats implanted and stimulated at a young age (Vollmer et al, 1999, Leake et al., 2000). Thus, temporal resolution does not seem to be a limiting factor for coding electrical signals in the central auditory system, even with severe peripheral pathology.

In this Quarterly Progress Report we present a preliminary draft of a manuscript reporting additional data from these valuable long-deafened animals, evaluating the spatial selectivity of electrical stimulation. Findings suggest that spatial selectivity in the IC is severely degraded and dynamic range is markedly reduced in long-deafened animals with severe cochlear pathology. Further, this effect was not reversed in the long-deafened animals that received a cochlear implant and several weeks of experience with intracochlear electrical stimulation,

Clinical studies have shown that there is great variability among human cochlear implant recipients in their speech recognition ability. In particular, congenitally deaf individuals implanted as adults generally demonstrate particularly poor speech discrimination, but they tend to improve gradually with increasing auditory experience. These individuals are likely to have relatively severe cochlear pathology, similar to the long-deafened animals in our recent studies. Our experimental findings in these subjects suggest that alterations in spatial (spectral) selectivity, rather than alterations in temporal resolution in the central auditory system, may be the limiting factor resulting in poorer speech discrimination performance in these prelingually deafened cochlear implant users.

INTRODUCTION

In contemporary multichannel cochlear implants (CI), the selective activation of neural populations is an important factor for the functional independence of channels. Psychophysical studies in human CI users have demonstrated that greater channel interaction is negatively correlated with the ability to rank the pitch of individual CI channels (Townsend et al. 1987) and also with poorer speech discrimination performance (Chatterjee and Shannon 1998, Throckmorton and Collins 1999, Henry et al. 2000, Zwolan et al. 1997).

Particularly poor speech discrimination performance is observed in congenitally and prelingually deaf CI users who are implanted as adults (Busby et al. 1991, Ruben 1986). However, it is unclear at present to what extent these observations are due to peripheral pathology or to functional changes in the central auditory system.

Animal studies have shown that sensorineural hearing loss before the onset of hearing or during early postnatal periods results in more profound anatomical degeneration (e.g., Moore 1990; Nishiyama et al. 2000; Nordeen et al. 1983) and functional degradation or reorganization as compared to changes observed following auditory deprivation later in life (e.g., Hardie et al. 1998; Hardie and Shepherd 1999; Moore 1994; Raggio and Schreiner 1999; Shepherd et al. 1997; Silverman and Clopton 1977; Trune 1982).

At UCSF, we have developed a deaf animal model of neonatal deafness to evaluate the effects of early auditory deprivation and the duration of deafness on signal processing in the central auditory system. These studies have demonstrated that 1) neonatal long-term deafness in cats results in very severe peripheral pathology with survival of less than 10% of spiral ganglion neurons; 2) such long-term deafness results in degraded temporal resolution of neurons in the central nucleus of the inferior colliculus (ICC), but this effect is reversed by a period of stimulation delivered by a cochlear implant (Vollmer et al. 2005); and 3) spatial selectivity of electrical stimulation is also significantly degraded in long-deafened animals (Rebscher et al. 2001, Vollmer et al. 2000).

The present study evaluates the effects of neonatally induced profound hearing loss and duration of deafness on spatial selectivity of intracochlear electrical stimulation (ICES) in the central auditory system. It extends the previous work by additional analyses of data from neonatally deafened animals that were studied after very long durations of deafness resulting in severe cochlear pathology, and includes data from a second group of these long-deafened animals that received a cochlear implant and underwent several weeks to months of unilateral electrical stimulation of the cochlea.

The results indicate that long-term auditory deprivation and severe peripheral pathology result in significant degradation of the spatial selectivity of ICES in the central auditory system, and this effect is not reversed by a period of experience of electrical stimulation with a cochlear implant. Similar alterations in spatial (spectral) selectivity likely contribute to poorer speech discrimination performance in prelingually deafened human cochlear implant users who are implanted as adults.

METHODS

Deafening and Implantation: Table 1 summarizes the deafness and chronic stimulation histories of the individual neonatally deafened animals included in the present study. Prior to all surgical procedures, the animals were sedated (ketamine: 22-33 mg/kg; acepromazine maleate: 0.1 mg/kg; or inhaled isoflurane), and anesthesia was induced by pentobarbital sodium (7-10 mg/kg) delivered via an intraveneous catheter. An areflexic level of anesthesia was maintained by intraveneous infusion of pentobarbital sodium in Ringer's solution. In the present study, all procedures followed NIH and UCSF IACUC guidelines for the care and use of laboratory animals.

Animal ID	Age @ Initital Stimulation (mo)	Duration of chron. Stimulation (wks)	Age at Study (mo)	Spiral Ganglion Survival (% normal)	Stimulation Characteristics
Short Deafened Unstimulated (SDU)					
K11	NA	NA	8	42.52	NA
K26	NA	NA	14	23.5	NA
K30	NA	NA	7	55.6	NA
K44	NA	NA	6	64.4	NA
K46	NA	NA	9	40.3	NA
Mean			46.5	45.26	
Long Deafened Unstimulated (LDU)					
K03	NA	NA	31	3.1	NA
K16	NA	NA	44	4.5	NA
K24	NA	NA	30	3.1	NA
K33	NA	NA	51	5.1	NA
K51	NA	NA	78	4.9	NA
K73	NA	NA	38	18.3	NA
K111	NA	NA	38	11.9	NA
Mean			44.29	7.27	
Long Deafened Stimulated (LDS)					
CH611	42	28	50	3.1	300/30 SAM, 80 pps, SP; Beh
CH618	52	34	60	1.3	300/30 SAM, SP; Beh
CH539	65	13	69	2.7	SP, 300/30 SAM; Beh
K56	84	7	86	5.1	300/30 SAM; Beh
CD393	73	24	79	3.5	300/30 SAM
Mean	63.2	21.2	68.8	3.1	

TABLE 1: Summary of onset and duration of deafness, chronic stimulation history and behavioral training for the neonatally deafened animals included in this report.

This report includes results obtained from five neonatally deafened cats that were studied as adults after ≤1.5 yr of deafness (SDU animals) and twelve long-deafened (LD) animals (duration of deafness ≥2.5 yr). All SDU and LD animals were deafened as

newborns by systemic administration of neomycin sulfate (40-70 mg/kg im/SID) beginning 24 h after birth and continuing for the first 14-25 days after birth (Leake et al. 1987; 1991). Neomycin injections were terminated when profound hearing loss (>108 dB) was confirmed by the absence of auditory brainstem responses to clicks (0.2 ms/ph, 20 pps) and frequency following responses to tonal stimuli (500 Hz). None of the animals demonstrated any residual hearing at the time of study.

The LD animals were divided into two groups: Seven unstimulated cats received a unilateral cochlear implant as adults and were studied acutely (long-deafened unstimulated, LDU group). Two of the LDU animals (K16 and K24) were implanted immediately before study, the others were implanted at least 1 week before the electrophysiological experiment to allow thresholds to stabilize. Five LD cats were also implanted as adults and received several weeks to months of chronic electrical stimulation prior to study (long-deafened stimulated, LDS group). All LD animals were maintained for periods ranging from 2.5 to 7.2 years prior to study. Electrical stimulation of the auditory nerve in these animals was initiated at ages ranging from 3.5 to 7.0 years with an average age of 5.5 years.

Fourteen adult cats with normal auditory experience prior to the experiment served as controls. Control cats usually were deafened 1.5-3.5 weeks before study by intravenous administration of kanamycin and ethacrynic acid (Xu et al. 1993). About half of the control animals were implanted immediatley before the experiment, the others were usually implanted ~1-2 weeks before study.

Implantation. Cochlear electrodes were fabricated with 2 bipolar pairs of platinum-iridium wire electrodes embedded in a silicone rubber carrier and were implanted into the left scala tympani under general anesthesia using aseptic surgical procedures. Because of the large round window and expanded scala tympani in the hook region of the cat cochlea, we presume that the intracochlear position of the more basal electrode pair (3,4) relative to the modiolus was more variable. Typically the STC widths of electrode pair 3,4 tended to be broader and to have greater intersubject variability than those observed for the more apical electrode pair (1,2). Consequently, only data from stimulation with the apical electrode pair are reported in the present study. The stimulating contacts (~290 um in diameter) comprising the apical electrode pair were arranged in an offset-radial orientation and were located on average at 49% (electrode #1) and 45% (#2) of basilar membrane distance from the cochlear base. Thus, in the normal cochlea the stimulating electrodes would have represented frequencies of about 5 to 6.3 kHz.

Chronic stimulation. Chronic electrical stimulation was applied for 4 h/d, 5 d/wk for a mean duration of 21 ± 11 (SD) wk. Electrically evoked auditory brainstem response (EABR) thresholds were determined as described previously (Moore et al. 2002), and chronic stimulation levels were set with maximum signal intensity adjusted to 2 dB above EABR threshold for each individual subject. All LDS animals were stimulated with the apical electrode pair 1,2. Due to lead failure, however, subjects CD393 and CH539 were stimulated with electrode pairs 2,3 and 1,4, respectively, during the final weeks of stimulation.

Electrical stimulation was delivered either by an analogue speech processor (SP) that transduced ambient environmental sounds into electrical signals delivered to the implanted electrodes or by computer-generated amplitude modulated pulse trains. For

stimulation with the SP, the frequency spectrum of the analogue stimulation was band-pass filtered from 250 Hz to 3 kHz with a roll-off at the shoulder frequencies of 6 dB/octave. The computer-generated signal was a continuous train of electrical pulses (200 μs/phase, charge-balanced biphasic square-wave pulses) delivered at a 300 pps carrier rate and sinusoidally amplitude modulated (SAM) at a frequency of 30 Hz with a modulation depth of 100% (300/30 SAM). The choice of these stimuli was based on previous studies showing that chronic electrical stimulation of the *developing* auditory system using these signals resulted in a significant increase in temporal resolution of IC neurons (Snyder et al. 1995; Vollmer et al. 1999).

One animal (CH611) received initial stimulation with an unmodulated pulse train at 80 pps that was delivered by a backpack stimulator for a period of two weeks. This animal did not tolerate stimulation outside its home cage, and the 80 pps stimulation was used until an analogue SP became available as a backpack stimulator for use in the home cage.

All but one cat received additional stimulation during behavioral training sessions (5d/wk; see Table 1). The total duration of suprathreshold stimulation during the behavioral sessions was very brief (a total of usually <30 s) and, therefore, very limited compared to the duration of chronic passive stimulation (4h/d at suprathreshold level).

Electrophysiological procedures.

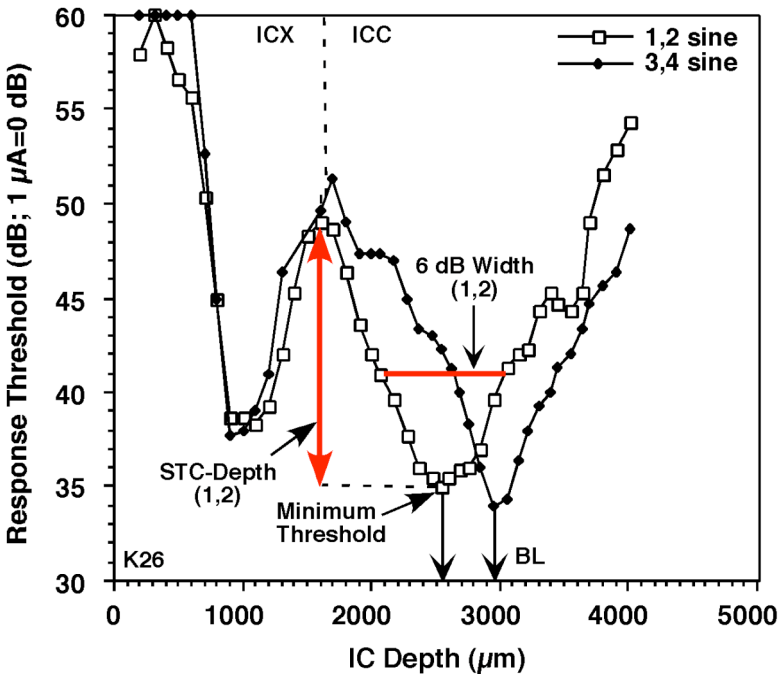

Figure 1. Threshold vs. depth functions in the IC or spatial tuning curves (STCs) for 3 cycles of a 100 Hz sinusoidal stimulation delivered on the apical electrode pair 1,2 (open symbols) and on basal electrode pair 3,4 (closed symbols). Because of the precise tonotopic organization of the ICC, the location of minimum threshold in the ICC for stimulation of each electrode pair provides a relative measure of the characteristic frequency and is defined as best location (BL). The high threshold region between the two locations of minimum threshold indicates the border between the two nuclei (dashed vertical line) and allows neurons in a given penetration to be assigned to either external or central nucleus.

The red horizontal line denotes 6 dB width for electrode pair 1,2; the red vertical line indicates tuning depth for pair 1,2 (difference between minimum threshold and higher threshold at border between ICX and ICC).

Electrically evoked auditory brainstem response (EABR) thresholds were estimated for each subject, and final acute electrophysiological experiments were conducted using tungsten microelectrodes to record responses of multi-neuronal clusters and single neurons in the IC. Several penetrations through the IC were made and response thresholds were recorded at intervals of 100 μm. Responses to biphasic electrical pulses (0.2 ms/phase) and to three cycles of a 100 Hz sinusoid were recorded, and the intensities intensities just sufficient to activate the neuron(s) were determined using audio-visual criteria. Thresholds were plotted as a function of IC depth along the tonotopic gradient of the IC to obtain spatial tuning curves (STC; Fig. 1). As reported previously, STC were typically W-shaped (Vollmer et al. 1999). The highest threshold region between the two locations of minimum thresholds was defined as the border between the two nuclei (see vertical dashed line in Fig. 1) and allowed neurons to be assigned to either external (ICX) or central nucleus of the IC (ICC). The widths of the spatial tuning curves were measured at 6 dB above the minimum ICC threshold for sines and at 2 dB and 6 dB above minimum ICC threshold for pulses in order to evaluate the extent of excitation across the tonotopic gradient (spatial selectivity/tuning). In addition, the difference between minimum ICC threshold and the higher threshold at the border between ICX and ICC were determined to study the tuning depth as an estimate of the neural dynamic range for activation of the IC with electrical stimulation (Fig. 1). At suprathreshold intensities that exceed the tuning depth, major continuous regions of both ICX and ICC are activated.

Histology.

After completion of the electrophysiological experiment, the cochleae of all long-deafened animals were prepared for histological analyses. The methods for the preparation of cochlear specimens were identical to those described by Leake et al. (1999) and will be described here only briefly. The cochleae were perfused, decalcified briefly, embedded in LX resin and mounted on glass slides as block surface preparations. Semithin sections (1-2 μm) were taken at 2 mm intervals along the basilar membrane and stained with toluidin-blue to assess the condition of the organ of Corti and the survival of SGC. SGC density in Rosenthal's canal was determined using a point-counting method (Leake and Hradek 1988; Leake et al. 1999). Earlier studies in normal hearing animals using this method provided normative data for the cat spiral ganglion (Leake and Hradek 1988). These data served as a control reference in the present study and allowed the SGC density of the SDU and LD cats to be expressed as percent of normal.

RESULTS

Spiral Ganglion Cell Survival

All SGC densities reported in this study refer to the implanted left cochlea in each animal. Figure 2 illustrates examples of SGC survival in Rosenthal's canal at the 40-45% cochlear sector for control, SDU and LD animals.

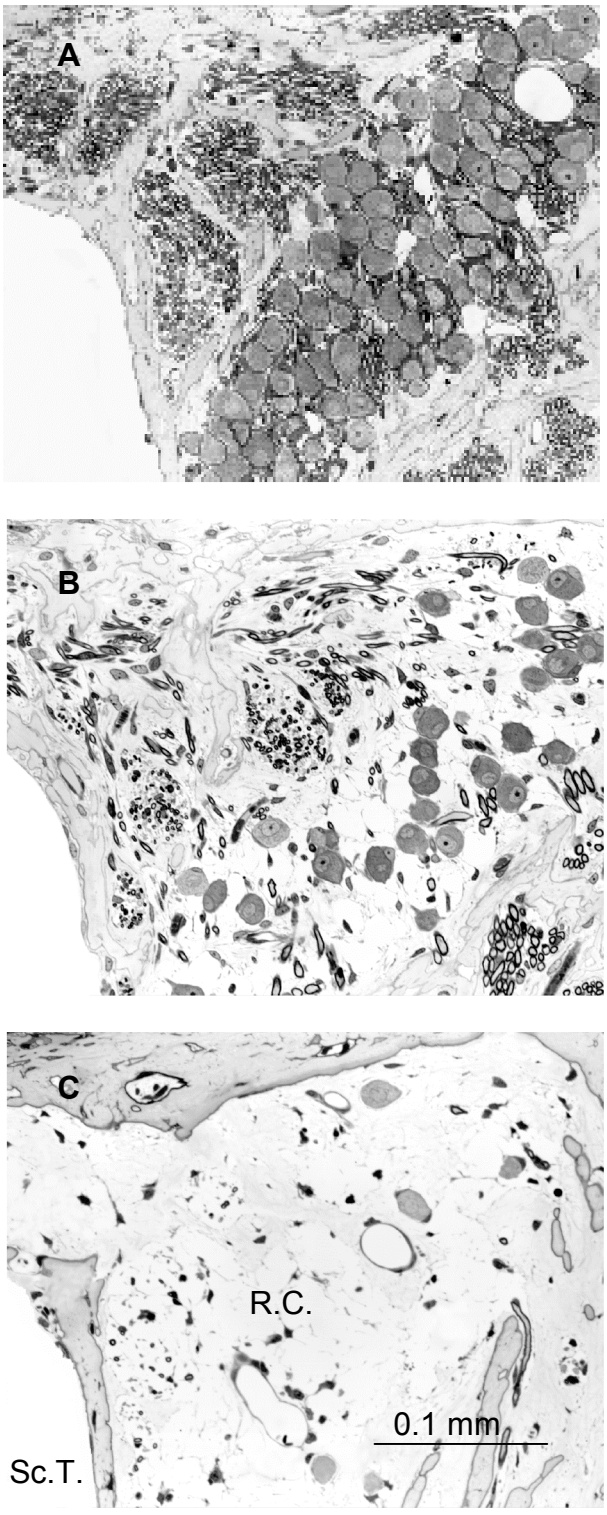

Figure 2. Rosenthal's canal at the 40-50% sector of the left cochlea in normal control (A), SDU (B) and LD (C) animals.

A. Densely packed, myelinated SGCs and auditory nerve fibers are seen in a normal hearing cat.

B. Partial degeneration of SGC and auditory nerve fibers is illustrated in a MLD animal.

C. Severe SGC loss is seen in Rosenthal's canal after long-term deafness. This image is taken form subject #K51 with a mean overall SGC density 4.9% of normal. Note also the shrinkage and demyelination of cell somata and the marked loss of auditory nerve fibers. Sc.T., scala tympani; R.C., Rosenthal's canal.

It is clear from the images in Figure 2 that the density of SGCs and auditory nerve fibers decreases with increasing durations of deafness. Table 1 and Fig. 3 summarize the quantitative data on density of SGC averaged across all cochlea sectors for the individual experimental cats. The data for each animal are expressed as percent of normal SGC density as described previously (Leake and Hradek 1988). The mean SGC density in the SDU group was ~45% of normal. The degeneration of SGC in the LD animals was significantly more severe. SGC survival in the LDU group was reduced to 7.9% of normal, whereas in the LDS group the mean SGC density was reduced to only 3.1% of normal. The difference in SGC survival between LDU and LDS was statistically significant (Student's t-test; $P<0.01$).

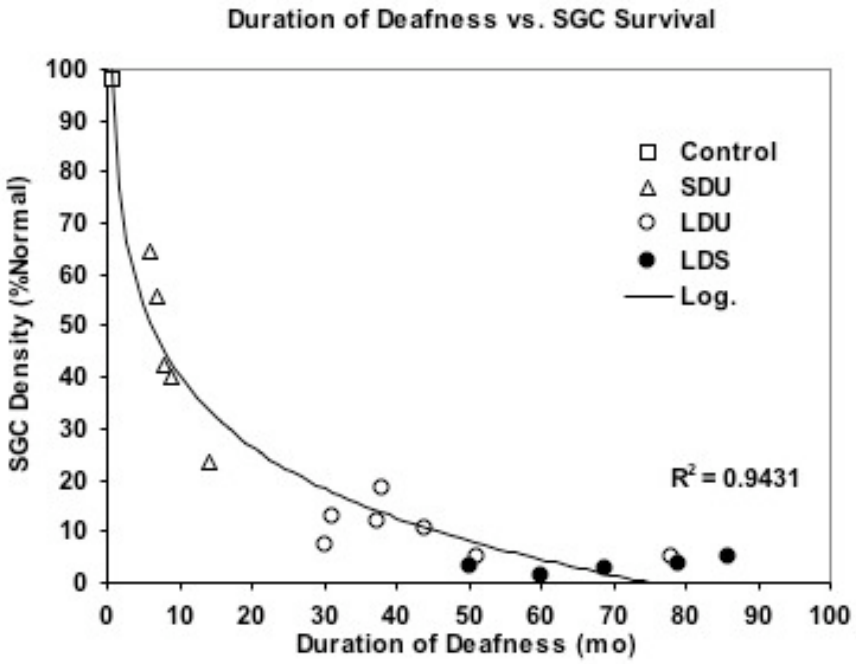

Figure 3. These data illustrate the progressive loss of SGC cells with increasing durations of deafness. Because of the small interindividual differences in SGC density and duration of deafness, the data from all control animals are combined in one symbol (□).

Somewhat greater survival was seen in one cat in the LDU group (K73) that had an average SGC density of 44% and 39% of normal in the 70-80% and the 80-90% sectors, respectively, and an overall SGC density of 18.3% (see Table 1). It is possible that this animal had, at an early stage after the deafening procedure, some residual hair cells and perhaps even some low frequency residual hearing that was missed with our standard ABR thresholds measures. With respect to the examining the effect of severe SGC degeneration on the physiological status of the central auditory system, given the higher SGC density in K73, the electrophysiological results in this animal must be interpreted with caution. The data from this animal have been removed from the statistical comparisons reported in this QPR, but are included in the scatter graphs of the raw data.

Response Thresholds

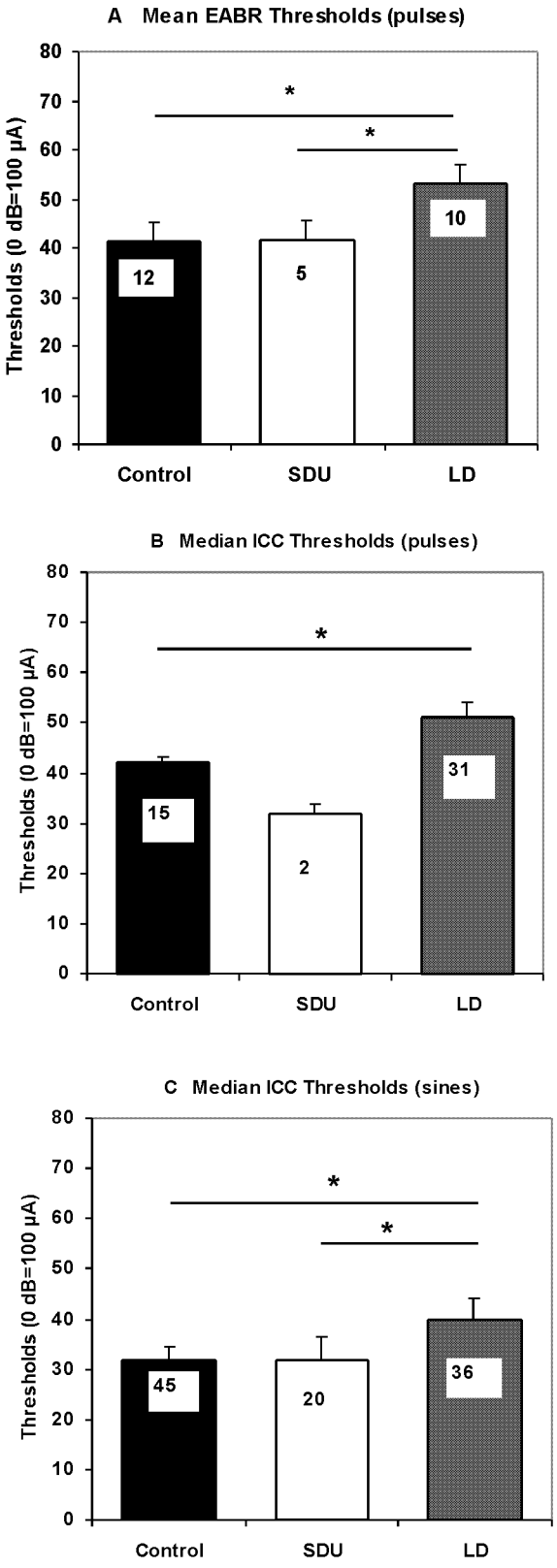

Figure 4. Threshold comparisons are shown for control, SDU and LD animals. Bars indicate standard deviation in (A) and quartile deviation in (B) and (C). Asterisk indicates statistical significance ($P<0.05$, one-way ANOVA in (A) and (C), t-test in (B)). Numbers on data bars indicate numbers of EABR and *minimum* ICC thresholds measurements included in the data set.

Results from LDU and LDS were pooled (LD group) when there was no significant difference between the two groups. Because ICC thresholds for pulses were available for only 2 subjects in the SDU group (B), this group was not included in the statistical comparisons.

In all three data sets, thresholds from LD animals were significantly higher than those of control subjects ($P<0.05$, t-test in B, one-way ANOVA for multiple comparisons in A and C). In addition, LD animals had significantly higher EABR and minimum ICC thresholds for sines than SDU animals.

Dynamic Range as Estimated by STC Depths

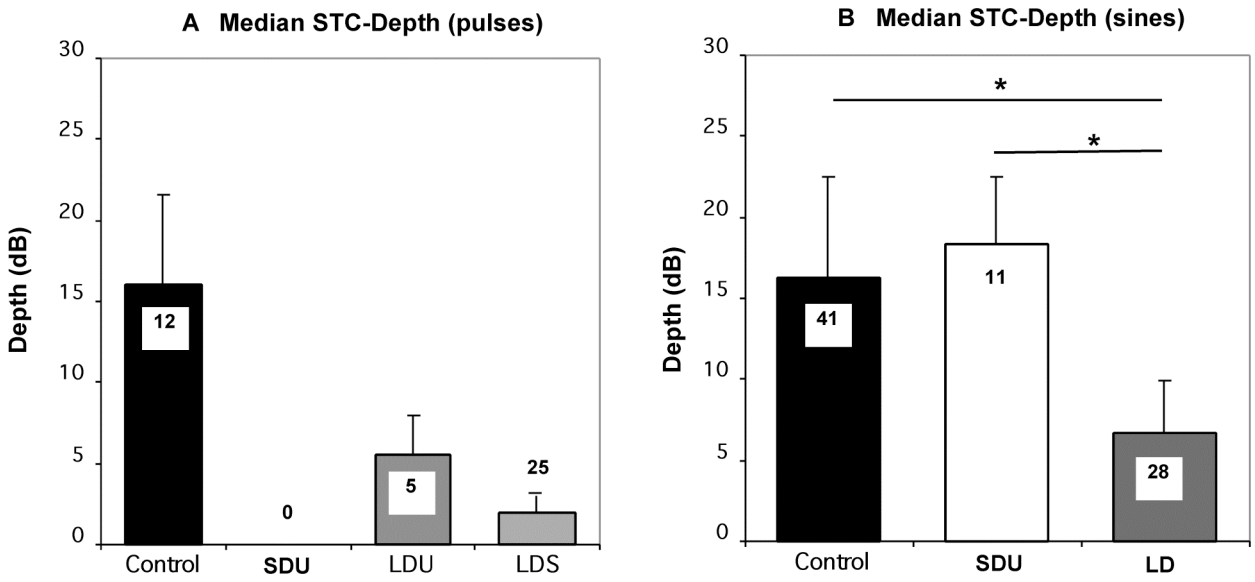

Figure 5. Median STC depths for pulsatile (A) and sinusoidal (B) stimulation. Bars = quartile deviation, *=statistical significance (P<0.05, one-way ANOVA). Numbers indicate number of single tuning curves that allowed a measure of STC-depth.

Due to the difference in charge per phase of the 100 Hz sinusoidal (5 ms/ph) and pulsatile (biphasic pulses, 0.2 ms/ph) signals, STCs obtained with sinusoidal stimuli generally had lower thresholds, markedly sharper tuning and greater depths (dynamic ranges) than those obtained with pulses. Figure 5 summarizes the median STC depths for pulsatile stimuli (A) measured at 2 dB suprathreshold and sinusoidal stimulati (B) determined at 6 dB above minimum threshold. Because STC widths tended to be very broad (Fig. 6) and dynamic ranges or STC-depths very small in long-deafened animals (Vollmer et al. 2000), a clear W-shape of the STCs and a border between ICX and ICC often could not be identified. As a consequence, the depths of STCs to pulsatile stimulation could not be determined in several of the long-term deafened animals, especially those in the long-deafened unstimulated group. Thus, because Figure 5A excludes such cases, it actually overestimates the STC-depths especially for LD animals. That is, dynamic range would be even more severely limited if there were a way to include cases in which the dynamic range was so small that the criteria established to define this measure were not met.

There is a significant difference in STC depths for pulses (Fig. 5A) between LDU and LDS animals. This result may be explained by the significantly longer duration of deafness, it may be confounded by the chronic stimulation of the LDS animals, or it may be a result of the large number of omitted STCs for which the depth could not be determined. Also, only limited data were available for the LDU group. Therefore no statistical multiple group comparison (ANOVA) was performed for pulsatile stimulation. Nevertheless, LD animals demonstrate a clear trend towards shallower STC depth and, thus a smaller dynamic range than control animals.

For stimulation with 100 Hz electrical sinusoids (Fig. 5B), there was no significant difference between STC depths measured for LDU and LDS animals. Therefore, the

data from the two experimental groups were pooled (LD animals). LD animals had significantly smaller STC depths than both control and SDU animals. There was no difference between control and SDU animals.

Selectivity of Activation and STC Widths

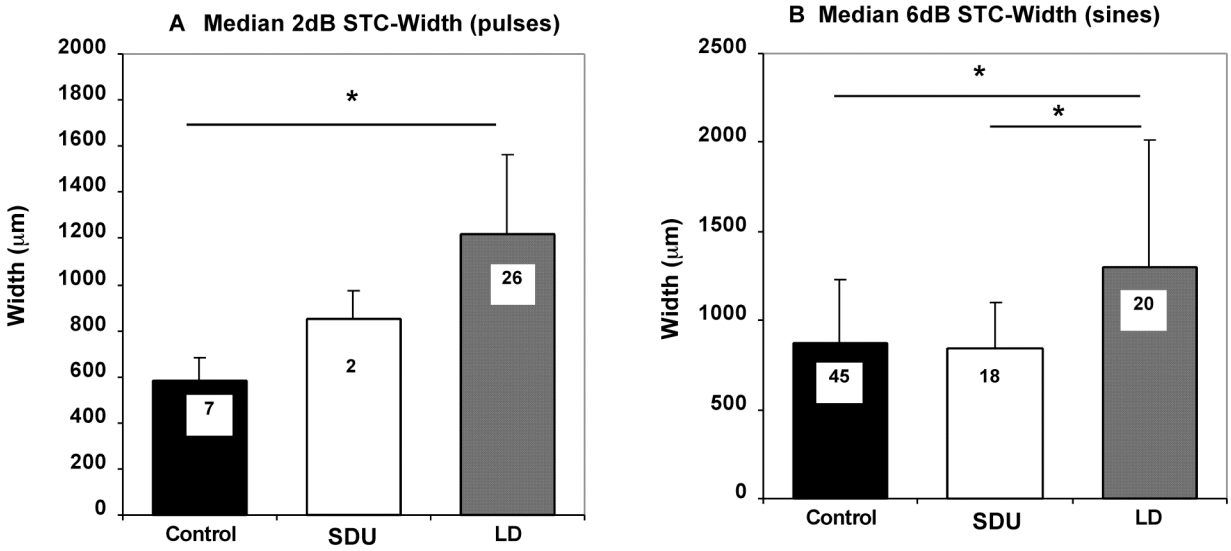

Figure 6. Comparisons of STC width measures across control, SDU and LD animals. STC widths were measured at 2 dB above minimum ICC pulse thresholds (A) and at 6 dB above minimum ICC thresholds for 100 Hz electrical sinusoids (B). Bars = quartile deviation, * indicates statistical significance ($P<0.05$, one-way ANOVA). Numbers indicate number of individual tuning curves that allowed a measure of STC-depth.

Measures of STC width reflect the extent of activation across the IC at a given intensity above threshold and thereby provide a measure of the selectivity of activation across the frequency gradient of the central auditory system that is elicited by a given stimulation condition. Figure 6A summarizes the median STC widths for stimulation with electrical pulses delivered at 2 dB above minimum threshold for the electrode pair 1,2. SDU data were not included in the statistical analysis because of the small number of available measures (n=2). LD animals have significantly broader extent of excitation compared to control animals ($P<0.05$, t-test). Moreover, as described above, the median STC width for the LD animals may be underestimated because STC depths in these animals were often smaller than 2 dB for pulsatile stimulation, in which cases exact estimates of STC widths were not possible.

Figure 6B summarizes the median STC widths for sinusoidal stimulation at 6 dB above minimum threshold. Due to the longer phase duration of this signal (10 ms/ph) minimum thresholds are typically lower, STCs are typically deeper and have a larger dynamic range than those for pulsatile stimulation (0,2 ms/ph). These characteristics of the sinusoidal STCs allow an easier determination of the ICX/ICC border and of STC width. For sinusoidal stimulation, there was no significant difference in spread of activation (as measured by the STC widths) between control and SDU animals.

Therefore, the two groups were combined for statistical comparisons. The LD animals had significantly broader 6 dB STC widths than both SDU and control animals ($P<0.05$, one-way ANOVA).

Figure 7 illustrates a strong negative correlation between STC-width and STC-depth for sinusoidal stimulation (correlation coefficient R = 0.695). These results indicate a systematic relationship between shallower STCs (measured at 6 dB suprathreshold) and broader spread of activation. STC depths are particularly shallow in LD animals, suggesting that greater channel interaction would occur in these animals. Conversely, relatively selective or narrow STC have greater neural dynamic ranges.

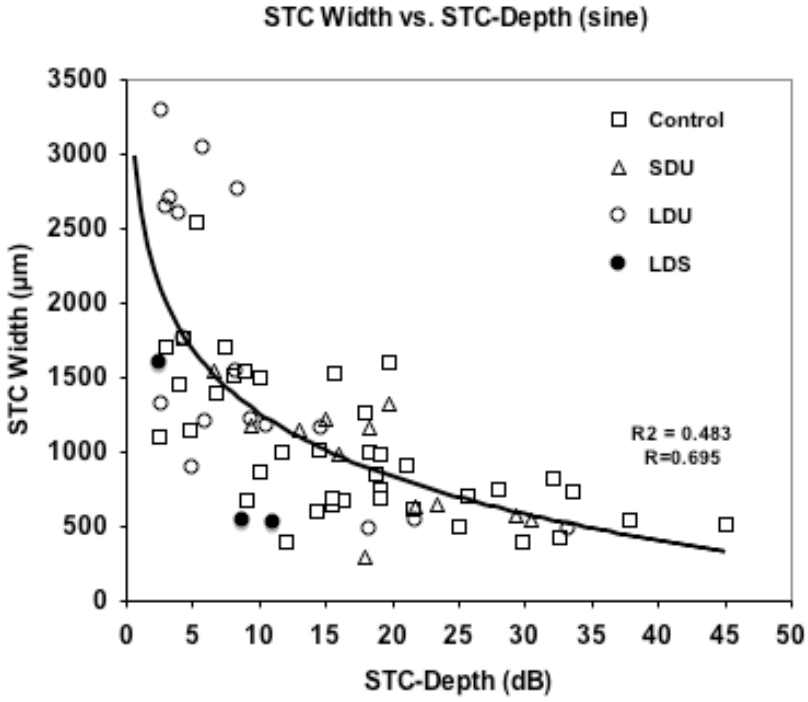

Fig. 7. STC widths derived from stimulation with a 100 Hz electrical sinusoidal stimulus are plotted against STC depth for the same tuning curve. Curve = logarithmic regression line. Broader STC width, indicating broader extent of excitation of the IC is correlated with smaller values for STC depths, indicating a smaller neural dynamic range.

SUMMARY AND CONCLUSIONS

The present results suggest that long-term auditory deprivation can effectively alter the representation and processing of intracochlear electrical signals in the central auditory system. Long-term deafness (>2.5 years) resulted in severe loss of SGC, significant increases in thresholds and marked degradation in both the spatial selectivity (STC width) and neural dynamic range (STC depth) of electrical stimulation in the central auditory system. These parameters are important factors in determining channel interaction in multi-channel implants and may contribute to the overall poorer speech discrimination performance in prelingually deafened CI listeners who were implanted as adults after long durations of deafness.

In contrast, more moderate durations of deafness (<1.5 yr) did not alter spatial selectivity of electrical stimulation in the central auditory system. However, it is not clear at present to what extent early chronic stimulation can prevent, or may even cause, negative effects on spatial selectivity and, thus, channel interactions.

The finding in our prior study demonstrating that degraded temporal resolution in long-deafened animals is reversed by a period of electrical stimulation of the cochlea with an implant suggests that temporal resolution likely is not a limiting factor in coding of central coding of electrical signals, even with very severe cochlear pathology. The degraded spatial selectivity in these same subjects as demonstrated in the current study, indicates that the spatial (spectral) resolution is severely limited with very severe cochlear pathology. Together, the findings suggest that poorer speech discrimination performance in prelingually deafened human cochlear implant users who are implanted as adults is likely limited more by the spatial (spectral) resolution rather than by the temporal coding capacity of the central auditory system.

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WORK PLANNED FOR NEXT QUARTER

1) Two subjects that had completed chronic electrical stimulation were studied during this past quarter in terminal acute electrophysiological studies recording from the inferior colliculus and primary auditory cortex. One of these subjects was an animal deafened at 30 days of age (See 2 below); the second subject was a neonatally deafened, single channel stimulation subject. The data from this subject are needed to strengthen statistical findings for a publication correlating IC and AI temporal following in control, chronically-stimulated, and long-deafened animals. These analyses, and hopefully a draft of the manuscript, should be completed during the coming quarter.

2) Data analyses of spiral ganglion survival, and cochlear nuclear morphology along with electrophysiological data will continue in the new experimental group of subjects that have been deafened at 30 days rather than neonatally (including the new subject studied acutely last month). The goal of this series to examine possible critical periods in the anatomical effects of deafness and chronic electrical stimulation on the cochlea and cochlear nucleus.

3) During this next quarter, a normal adult cat will be studied in an acute electrophysiological experiment utilizing the 32-channel NeuroNexus probes. A brief acoustic calibration procedure will be conducted during which a penetration site in the IC is selected and an ideal penetration depth is determine based on the range of characteristic frequencies recorded, which must comfortable encompass the range of frequencies accessed by the intracochlear implant electrode. Next, the animal will be deafened by an injection of kanamycin followed by infusion of ethacrynic acid to effect, as indicated by elevation of ABR thresholds. Finally, an 8-channel UCSF cat electrode will be implanted and responses to electrical stimuli will be recorded. Data collection will focus on electrical spatial tuning curves and masking protocols.

4) Although it is late in the year for the normal breeding season, we are hoping that one of our female cats is pregnant (pregnancy test on Nov. 2). If so, one kitten will be deafened at 30 days of age, and implanted as part of this new series. During the current quarter, one subject in this series damaged his device failed to meet the criterion 6 months of stimulation. Although the data from this subject will still be usable, we would like to have one more subject complete the full protocol. In addition, if a litter is available 2 kittens will be studies in a pilot experiment to examine the effects of BDNF on spiral ganglion survival by infusing BDNF directly into the cochlea in neonatally deafened animals. This pilot study is a first step toward eventually evaluating the effects of combined BDNF treatment and electrical stimulation of the cochlea.

5) Studies of the human cochlea will continue, with current analyses directed toward refining mathematical functions that will define represented frequency along both the organ of Corti and spiral ganglion as a function of angle of rotation from the round window.