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Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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This QPR is being sent to you before it has been reviewed by the staff of the Neural Prosthesis Program.

ABSTRACT

[illegible] presents results documenting the effects of intracochlear electrode [illegible] function of monopolar electrode orientation and separation [illegible] experiments conducted in 13 normal adult cats and [illegible] adult cats. Each animal was implanted with a five contact intracochlear [illegible] intracochlear electrical stimulation with several electrode [illegible] recorded in the contralateral inferior colliculus. EABR responses were [illegible] group consisted of animals that were deafened [illegible] Prior to [illegible] neonatally deafened animals were studied at ages ranging from 6 months [illegible] configurations studied included 2 monopolar intracochlear electrodes [illegible] mm offset radial bipolar and 4-6 mm longitudinal bipolar [illegible] evaluation of these data indicates that: (1) Monopolar thresholds are [illegible] lower than the lowest bipolar thresholds in all animals. (2) Varying [illegible] electrode separation of bipolar contacts from zero separation (radial) to [illegible] did not affect IC threshold in normal animals. The chronically deafened [illegible] a positive correlation in threshold as a function of increasing longitudinal [illegible] to preliminary results we found that monopolar stimulation [illegible] significantly wider spatial tuning in the IC than bipolar stimulation (when [illegible] above threshold). (4) Normal animals were more sensitive to changes in [illegible] position than chronically deafened animals, although this effect may be the [illegible] number of long deaf animals in which this parameter was examined. [illegible] configurations considered in this study the offset radial bipolar configuration [illegible] optimum electrode configuration for the greatest number of circumstances. [illegible] individual variability we believe that it is advantageous to maintain the [illegible] configure an implanted system to best fit each patient and to develop fitting [illegible] make this possible in the clinical setting.

[illegible] conclusions from this study are important to ongoing efforts to better [illegible] intracochlear electrical stimulation and the physiological mechanisms [illegible] this process. These include the following observations: (1) Spatial selectivity for [illegible] electrical stimulation remained normal in neonatally deafened animals for [illegible] 4 months. Spatial tuning was significantly degraded in animals with longer [illegible] deafness. (2) Minimum IC thresholds were not significantly higher in long [illegible] compared to the normal group. The EABR thresholds, however, [illegible] crease significantly in this group. (3) The presence or absence of peripheral fibers does not appear to significantly affect thresholds in most stimulating configurations.

Effects of stimulating electrode separation and location on the physiological responses to intracochlear electrical stimulation

The effects of electrode contact separation (measured longitudinally), contact orientation [illegible] the radial dimension on a cylindrical insulating carrier), stimulation strategy (bipolar vs. monopolar) and carrier location in the scala tympani have been discussed [illegible] previous progress reports submitted for this contract and for a past [illegible] Neuro sciences Contract #N01 DC [illegible] 2401 "Studies of Pediatric Auditory [illegible] [illegible]" see Final Technical Progress Report January [illegible] 1996 and earlier reports. The following report presents an update on these studies including the [illegible] several long term animals which were deafened as neonates and studied as adults [illegible] years of age. Table 1 summarizes the history, EABR threshold and [illegible] threshold for each animal studied and the average spiral ganglion [illegible] each chronically deafened animal. This report includes data from thirteen [illegible] deafened prior normal animals, four neonatally deaf animals studied [illegible] and seven neonatally deaf animals studied at ages greater [illegible]

Table [illegible] Animal Summary

[illegible] Number	Duration of Deafness Months Meth	Duration of Implant (Weeks)	Electrode Type	Spiral Gang Survival (% Normal) 90 [illegible] BM	EABR Thr Bipolar 1.2 200usec (uAmps)	[illegible] Thr Bipolar 1.2 100Hz sine (uAmps)
[illegible] Deafened Animals						
[illegible]	Kanamycin	[illegible] weeks	UCSF		[illegible]	[illegible]
[illegible]	Kanamycin	Acute	UCSF		50	45
[illegible]	Kanamycin	Acute	UCSF		50	22
40	Intracochlear	Acute	UCSF		50	[illegible]
[illegible]	Intracochlear	Acute	UCSF		63	[illegible]2
[illegible]	Intracochlear	Acute	UCSF		NA	32
50	Intracochlear	Acute	UCSF		63	32
[illegible]	Kanamycin	Acute	UCSF		158	22
[illegible]	Kanamycin	Acute	UCSF		316	56
[illegible]	2 Kanamycin	Acute	Queens		NA	100
[illegible]	Kanamycin	Acute	Queens		NA	45
[illegible]	Kanamycin	Acute	Wing		200	56
[illegible]	Kanamycin	Acute	Wing		63	5
Neonatally Deafened Animals (Less Than 1 yr of age)						
K[illegible]	8 neomycin	Acute	UCSF	NA	100	50
K30	[illegible] neomycin	20 weeks	UCSF	NA	100	40
K44	6 neomycin	10 weeks	UCSF	27.2	100	14
K46	8 neomycin	Acute	UCSF	17.1	100	14
Long Deafened Animals (More than 1 Year of Age)						
K03	31 neomycin	2 weeks	UCSF	13.1	398	126
K16	44 neomycin	Acute	UCSF	10.7	126	45
K24	30 neomycin	Acute	UCSF	7.2	251	50
K26	14 neomycin	3 weeks	UCSF	23.5	200	50
K33	31 neomycin	1 week	UCSF	5.1	251	112
K[illegible]	78 neomycin	6 weeks	Wing	4.85	398	56
K7[illegible]	41 neomycin	2 weeks	Wing	18.3	126	14

Methods

As described in earlier reports, long deafened animals were neonatally deafened with daily subcutaneous injections of neomycin sulfate (50 or 60 mg/kg) for [illegible] days. At this time the ABR threshold and EFR threshold to a 500Hz tone was measured for each animal up to the output limits for the acoustic source (approximately 115 dB SPL [illegible] speaker). In most cases no acoustic reponse was present. In those cases in which an ABR or EFR response was recorded at sixteen days the neomycin injections were continued for an additional five days and these animals were retested. No responses were observed at this twenty one day test for any of the animals [illegible]. These deafened animals were maintained without complication for periods of up to [illegible] years prior to implantation and the final physiology experiment. Four adult animals were deafened unilaterally by intracochlear injection of neomycin to permit simultaneous recording of acoustic responses from the contralateral ear. The remaining adults were deafened with a single subcutaneous injection of Kanamycin (400mg/kg) followed by a single injection of aminooxyacetic acid (25mg/kg). ABR and EFR responses were tracked in these adult animals throughout the deafening procedure and no responses were observed. In most cases adult animals were deafened one to two weeks prior to the physiology experiment and implanted at the time of the experiment. In some cases the animals were either deafened or implanted for longer periods before the final experiment. These exceptions are indicated in Table I. Normal animals #2[illegible] and #[illegible]2 received some extracochlear electrical stimulation in a behavioral training apparatus prior to study in these intracochlear electrical stimulation experiments. All other animals recieved no electrical stimulation prior to the acute physiology experiment.

Each animal was implanted with a multichannel intracochlear electrode in the [illegible] cochlea. The latest version of the UCSF intracochlear electrode is shown in Figure 1. The electrode consists of an injection molded silicone rubber carrier which held five Pt-Ir electrode contacts 225um diameter for these experiments. This electrode tapers from slightly larger than 1 mm at the basal contact set to 0.5 mm at the tip. The enlarged cross section near the round window and the small fins along the more apical electrode body were designed to improve the position of the electrode carrier within the scala tympani and to partition the volume of conductive fluid adjacent to the electrode.

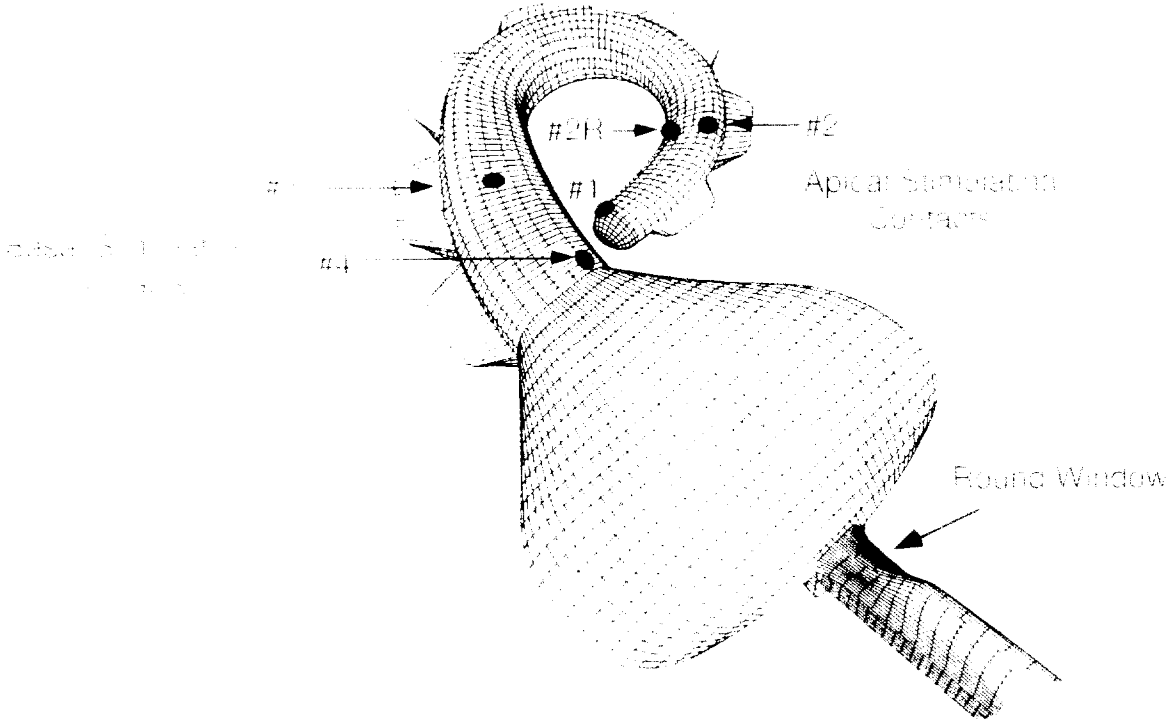


Figure [illegible] experiments described in this report were conducted with three different [illegible] electrode designs. In most cases (8 animals) the UCSF feline electrode was used [illegible] described. The most recent UCSF feline electrode shown above was used in the [illegible] additional experiments were conducted with a similar intracochlear [illegible] at Queen's University. In each case the main electrode carrier was a cylindrical [illegible] silicone rubber 7 to 8 mm in length holding up to seven (7) [illegible] stimulating [illegible] the carrier.

[illegible] UCSF feline electrode consisted of a simple cylindrical carrier [illegible] from [illegible] mm at the round window to 0.6 mm at the tip. The Queen's University electrode was similar to the original UCSF feline electrode with one large projecting [illegible] from the lateral edge of the molding. A top view of these three electrode designs is shown in Figure 2.

In each case the positions of electrode contacts used for this study were similar. For measurements with radial electrode pairs a second contact was placed adjacent to an existing contact site. In the original UCSF electrode the radial contact was placed adjacent to the most apical contact position (numbered contact #1A in previous reports) and in the Queen's University electrode, which was used in two experiments, the radially placed contact (designated #2R) was adjacent to the second contact and was [illegible] mm basal to the most apical stimulation site. In the later UCSF electrode shown in Figure [illegible] the radial contact (#2R) was also positioned facing the medial wall of the scala tympani [illegible] mm basal to the most apical contact. In each case the radial electrode pair consisted of two contacts positioned with approximately 90-120° radial separation (center to center separation of approximately 550µm, 250 - 350µm edge to edge). Also in each case the offset radial configurations consisted of two electrode contacts with 1.0

[illegible] separation and 90° of radial separation. In the [illegible] offset radial [illegible] the apical contact (#1) of the offset radial pair was positioned [illegible] and the more basal contact (#2) was positioned [illegible] In all electrodes the basal offset pair [illegible] longitudinal separation. In this case the apical [illegible] contact #[illegible] the basilar membrane and the basal contact (#4) [illegible]. The electrode position data for each [illegible]

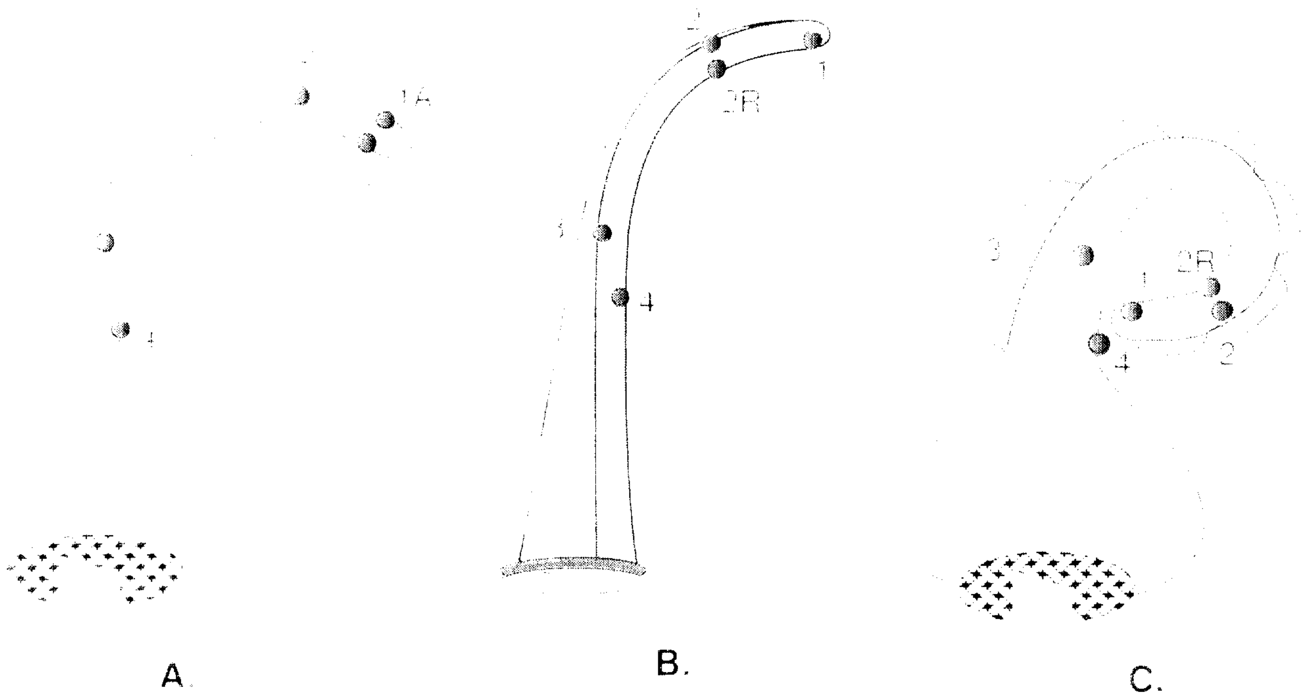


Figure 2. [illegible] electrode designs used in this study are illustrated above. Each [illegible] radial contact pair and offset contact at the tip of the [illegible] from the tip. [illegible] contact spacing is shown below.

Table 2. Electrode Contact Position Data

		Electrode Type		
		UCSF	Queen's	UCSF "Wing"
Number of Animals		n=18	n=2	n=4
Longitudinal Separation (Apical Offset Pair)		1.0 mm	1.0 mm	1.0 mm
Long. Sep. (Apical Contact #1 to Basal #4)		4.0 mm	5.0 mm	6.0 mm
Total Electrode Length		7.0 mm	8.0 mm	9.0 mm
Distance from Electrode Tip	Contact #1	0.2 mm	0.1 mm	0.0 mm
	Contact #1A	0.2 mm		
	Contact #2	1.2 mm	2.1 mm	2.0 mm
	Contact #2R		2.1 mm	2.0 mm
	Contact #3	3.2 mm	4.1 mm	5.0 mm
	Contact #4	4.2 mm	5.1 mm	6.0 mm

[illegible] physiological experiments conducted with these animals have been [illegible] previous progress reports (see also Snyder RL et al 1990, Hearing Research [illegible]). Briefly, animals were sedated with ketamine, an IV catheter was [illegible] and sodium pentobarbital was administered to induce an [illegible] anesthesia. The animals were continuously monitored and maintained [illegible] throughout the experiment. A craniotomy was performed to access [illegible] and the tentorium was opened to expose the inferior colliculus [illegible] implanted ear. EABR responses were recorded to assess electrical stimuli [illegible]. Recordings from the inferior colliculus were made using [illegible] electrodes. The trajectory of these electrodes were oriented so that they [illegible] inferior colliculus perpendicular to its tonotopic organization. The [illegible] of each stimulating electrode combination at each recording [illegible] was determined audiovisually. In cases where single units were [illegible] discriminated from multiunit activity the responses were recorded as [illegible] histograms. Response thresholds were plotted as function of IC [illegible] spatial tuning curve which describes the spatial spread of neural activity [illegible] tonotopic organization of the inferior colliculus. A typical plot for one [illegible] is shown in Figure 3 below. Peak to peak current measurements are [illegible] dB= 100 μAmps.

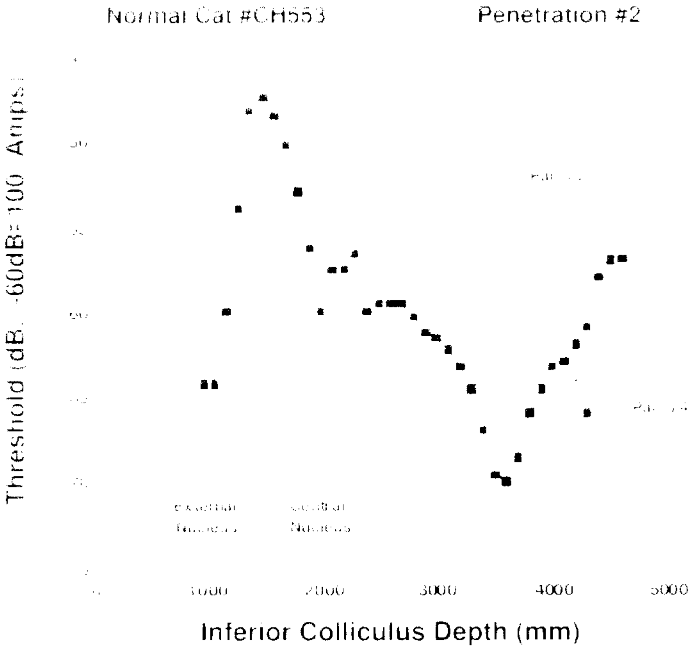


Figure 3. Response thresholds for intracochlear electrical stimulation using two electrode pairs, an [illegible] pair (1/2) and a basal pair (3/4). The minimum threshold region for the apical stimulating pair [illegible] superficially (i.e. in a lower frequency region) in the IC and the responses to the basal stimulating pair are located deeper (in a higher frequency region of the IC). The width of these spatial [illegible] was measured at 6 dB above the minimum threshold for each curve.

Results

Normal Animals - Table [illegible] summarizes the average minimum I[illegible] response [illegible] radial bipolar, offset radial bipolar and longitudinal bipolar [illegible] as measured in the acutely deafened, prior normal animals. In this group, the [illegible] threshold to monopolar stimulation ([illegible] dB [illegible]) is lower [illegible] bipolar configuration. In these comparisons responses to the basal [illegible] were not compared because of the differences in the [illegible] positioning of this basal pair.

Table 3 [illegible] Animals
[illegible] Longitudinal Separation

[illegible]	Number of Animals	Longitudinal Separation (mm [illegible])	Mean Threshold (dB)	Mean Threshold ([illegible]Amps)
[illegible]	n=8		74.8±8.5	[illegible]
[illegible]	n=8		73.7±8.8	[illegible]
Radial	n=6		68.2±9.1	[illegible]
Offset	n=10	1.0	67.0±7.7	[illegible]
Longitudinal	n=13	4.0 or 6.0	68.1±10.2	[illegible]

Table 4 presents statistical comparisons of ICC response thresholds for each [illegible]. Since all electrode combinations were not tested in all [illegible], these comparisons have been restricted to include only penetrations in [illegible] conditions were directly compared. These paired comparisons show a [illegible] significant difference between the monopolar condition (contact #1 or #2) and the [illegible] offset radial (pair 1-2) configuration. In contrast, there was no significant difference between the thresholds for the three different bipolar configurations.

Table 4 [illegible] Animals - Threshold
[illegible] Analysis of Paired Comparisons

		Threshold (dB)	Paired Student T Test	Significance (.05)
Primary Pair Comparison Pair	1-2 1 Mono	68.8 74.6	p=0.002 (n=8)	+
Primary Pair Comparison Pair	1-2 2 Mono	68.9 74.5	p=0.016 (n=8)	+
Primary Pair Comparison Pair	1-2 1-1a	69.9 68.2	p=0.08 (n=6)	-
Primary Pair Comparison Pair	1-2 1-4	67.5 68.1	p=0.3 (n=10)	-

[illegible] illustrates two series of exemplary STCs from individual animals [illegible] thresholds and the selectivity of stimulation elicited with various [illegible]. The difference in threshold between the monopolar [illegible] offset radial bipolar configuration is evident in Figure 4A as is the [illegible] for the three conditions of bipolar stimulation. Figure 4B

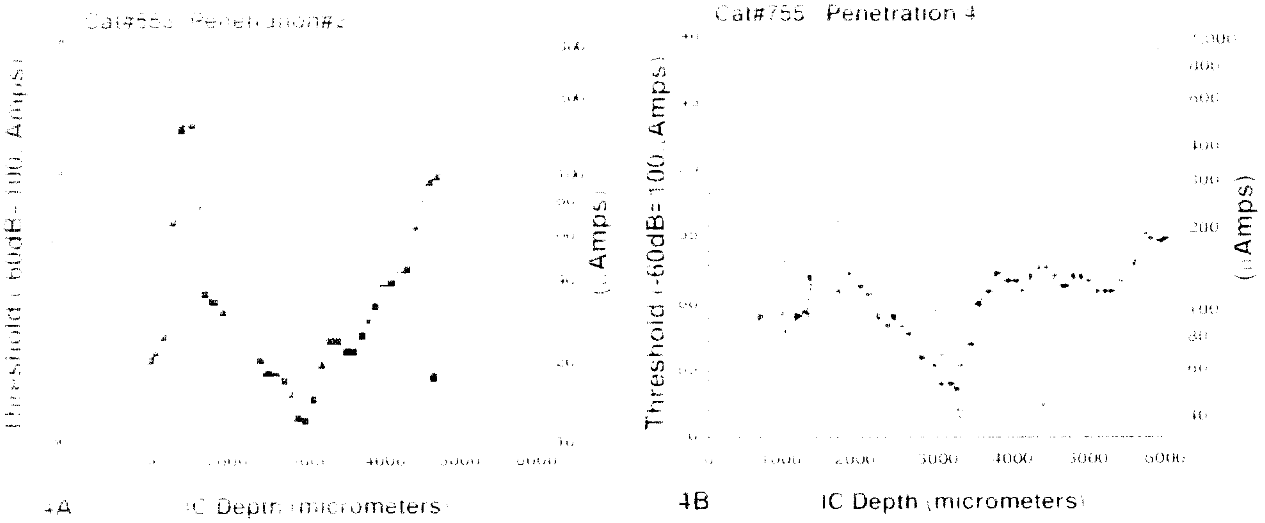


Figure 4 [illegible] STCs for monopolar and bipolar stimulus conditions are shown. Figure 4A [illegible] the offset radial bipolar pair [illegible] and the STCs from each contact as [illegible] penetration. In this example monopolar thresholds were an average of [illegible] offset bipolar combination. Figure 4B illustrates the responses to three [illegible] bipolar offset. As summarized in Table 4 there is no significant difference in [illegible] threshold produced with each of these three contact configurations. Although not [illegible] normal group of animals there is an orderly progression of increasing STC [illegible] and separation of stimulating contacts.

Table 5 summarizes the average STC widths at 6 dB above minimum threshold for [illegible] animals with monopolar and bipolar stimulus configurations. Although individual penetrations in some animals demonstrate quite narrow tuning for monopolar stimulation the overall mean STC width is somewhat greater with monopolar stimulation than with any bipolar combination.

Table 5 Normal Animals
Spatial Tuning Longitudinal Separation

Stimulus Sites	Number of Animals	Longitudinal Separation (mm c to c)	Mean STC Width (mm)
Monopolar	n=8		1.19±.57
2 Monopolar	n=8	-	1.30±.55
Radial	n=6	0.0	0.91±.49
2 Offset	n=10	1.0	0.80±.19
Longitudinal	n=13	4.0 or 5.0	0.97±.37

[illegible] paired comparisons tuning was sharper with a radial pairing than with the offset [illegible] longitudinally although this difference was not statistically significant (see [illegible] the offset radial configuration (1.0 mm longitudinal separation) [illegible] the longitudinal pairing (4.0-5.0 mm longitudinal separation) [illegible] difference was not statistically significant (p=0.08).

Table 6 [illegible] Spatial Tuning [illegible] Paired Comparisons				
		STC Width (mm)	Paired Student T Test	Significance (5%)
[illegible]	[illegible]	0.98		
[illegible]	Mon	1.19	p=0.02 (n=8)	*
[illegible]	[illegible]	0.93		
[illegible]	2 Mon	1.30	p=0.01 (n=8)	*
[illegible]	[illegible]	0.98		
[illegible]	[illegible]	0.87	p=0.14 (n=6)	
[illegible]	1,2	0.79		
[illegible]	1,4	0.97	p=0.06 (n=10)	

Long Deafened Animals - Minimum IC thresholds for monopolar and bipolar stimulation in long deafened animals are shown in Table 7. As also seen in the acutely deafened animals the mean threshold for monopolar stimulation was lower than that of [illegible] bipolar configurations (mean difference of 6.4 dB compared to offset pair 1,2). However, this difference was not statistically significant when thresholds were compared for matched pairs within penetrations (see Table 8).

Table 7 [illegible] Deafened Animals: Threshold, Longitudinal Separation				
Stimulus Sites	Number of Animals	Longitudinal Separation (mm c to c)	Mean Threshold (dB)	Mean Threshold (µAmps)
1 Monopolar	n=4	-	-73.0±10.4	22.0
2 Monopolar	n=4		-73.3±9.1	21.0
1a Radial	n=4	-	-61.6±9.9	79.0
1,2 Offset	n=11	1.0	-66.8±7.4	46.0
1,4 Longitudinal	n=9	4.0 or 5.0	-68.0±8.9	40.0

In contrast to the normal group, in the long deafened animals there was a statistically significant difference between the threshold for radial bipolar stimulation and offset radial stimulation (difference of 4.9 dB higher for the radial pair, p=.02). However, the difference between the offset pair (1,2) and the longitudinally separated pair (difference of 2.1 dB lower threshold for 1,4, p=.08) was not significant.

Table 8 [illegible] Deafened Animals
Statistical Analysis of Paired Comparisons

		Adjusted Threshold (dB)	Paired Student T Test	Significance [illegible]
[illegible]	[illegible]	[illegible]		
[illegible]	[illegible] Mono	[illegible]	p=0.2 [illegible]	
[illegible]	[illegible]	[illegible]		
[illegible]	2 Mono	[illegible]	p=0.06 [illegible]	
[illegible]	[illegible]	66.3		
[illegible]	[illegible]	61.6	p=0.02 (n=4)	*
[illegible]	1,2	66.6		
[illegible]	1,4	68.7	p=0.08 (n=8)	

[illegible] tuning width was broader for the long deafened animals as a group than [illegible]. As in the normal subjects, monopolar stimulation produced the [illegible] activation of the central nervous system. Among bipolar pairings the offset radial configuration demonstrated the most selective tuning, though not significantly more selective than the radial configuration. The longitudinal configuration (1,4) was significantly more broadly tuned than the offset radial configuration (1,2) in this group of animals. Tables 9 and 10 summarize the spatial tuning data for these chronically deafened animals.

Table 9 [illegible] Deafened Animals
Spatial Tuning: Longitudinal Separation

Stimulating Sites	Number of Animals	Longitudinal Separation (mm c to c)	Mean STC Width (mm)
1 Monopolar	n=4	-	1.97±.77
2 Monopolar	n=4	-	1.85±.48
1,1a Radial	n=4	0.0	1.76±.99
1,2 Offset	n=11	1.0	1.07±.57
1,4 Longitudinal	n=9	4.0 or 5.0	1.49±.90

Table 10 [illegible] Deafened Animals - Spatial Tuning
[illegible] Analysis (Paired Comparisons)

		[illegible] Width (mm)	Paired Student T-Test	Significance [illegible]
[illegible]	[illegible]	1.41		
[illegible]	[illegible]	2.00	p=0.04 (n=3)	
[illegible]	[illegible]	1.41		
[illegible]	2 Mon	1.88	p=0.03 (n=3)	
[illegible]	[illegible]	1.30		
[illegible]	[illegible]	1.77	p=0.21 (n=4)	
[illegible]	[illegible]	1.06		
[illegible]	[illegible]	1.36	p=0.02 (n=8)	

Comparisons Between Animal Groups. The data presented above can be [illegible] by comparing the responses generated by equivalent electrode [illegible] presented to the normal and neonatally deafened, chronic animals and [illegible] the SIC widths in the chronically deaf group based on the age of each animal. Because the peripheral auditory projections degenerate following deafening we expect the age of these chronic animals to correlate with the number of functional spiral ganglion neurons present in the cochlea.

[illegible] compares the mean response threshold for each stimulating condition for the [illegible] and neonatally deafened animals. Interestingly, despite very significant differences in [illegible] survival (see Table 1) the IC response thresholds to all but the [illegible] configuration were nearly identical between the two groups.

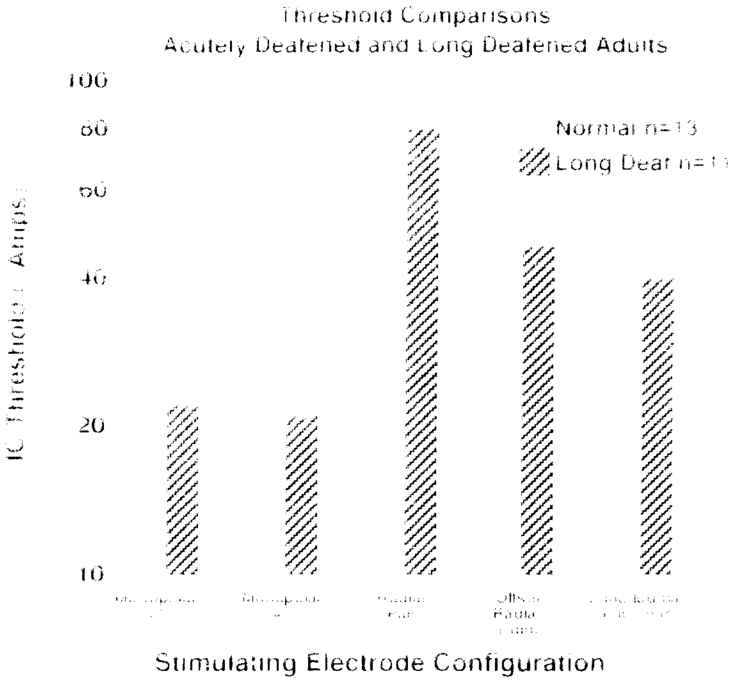
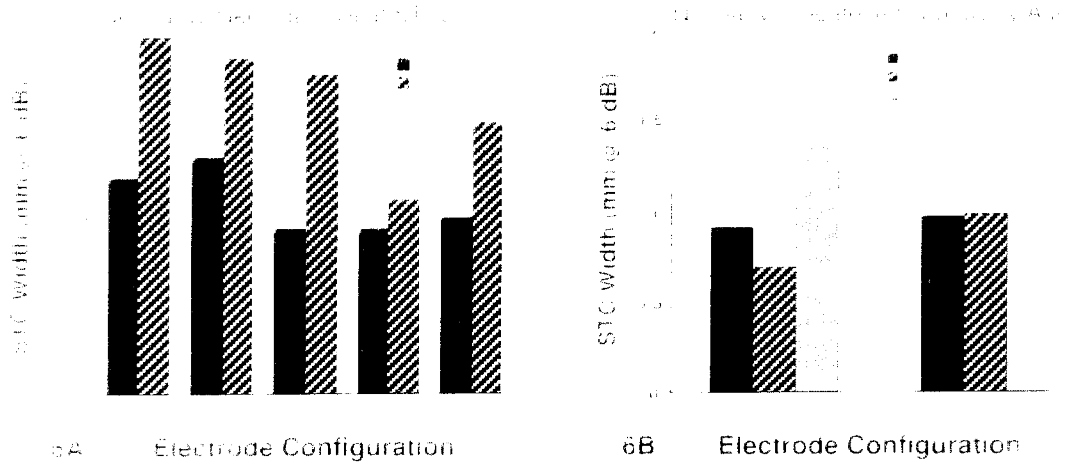


Figure [illegible] thresholds for each stimulus condition in the normal and long deafened [illegible] Except for the increase in response threshold to radial [illegible] deafened animals the thresholds between the two groups were very similar.

[illegible] compares the spatial tuning measured in the two groups of animals. [illegible] configuration the distribution of responses was broader in the [illegible] deafened animals than in the normal group. However, we observed two [illegible] patterns of spatial representation within the deafened group. Figure 6b [illegible] STC widths for normal animals with those of the deafened animals separated into [illegible] groups based on age and duration of deafness. The first group includes [illegible] less than one year of age at sacrifice. Animals that were older than one year at the time of the physiology experiment were placed in the second group. Unfortunately, [illegible] data are available for either the monopolar or radial bipolar configurations [illegible] the younger group of animals. Thus, this comparison includes only the offset radial bipolar and longitudinal bipolar conditions. In each of these paradigms the STCs from chronically deafened animals less than one year of age were very similar to those of normal animals. In contrast, the spatial selectivity measured in the older group of neonatally deafened animals was significantly broader compared to either the prior normal group or the younger neonatally deafened population.



[illegible] measured for each electrode configuration in the [illegible] and [illegible] neonatally [illegible] compared to [illegible] for each configuration the [illegible] the deafened [illegible] that the younger animals are [illegible] Neonatally [illegible] significantly less selective tuning.

[illegible] decrease in spatial resolution is clearly illustrated by plotting STC width as a [illegible] of deafness (see Figure 7). Spatial tuning in animals up to one year [illegible] unchanged. In fact, these animals all fall at or below the mean STC width [illegible] older animals demonstrate a roughly linear decrease in spatial [illegible]

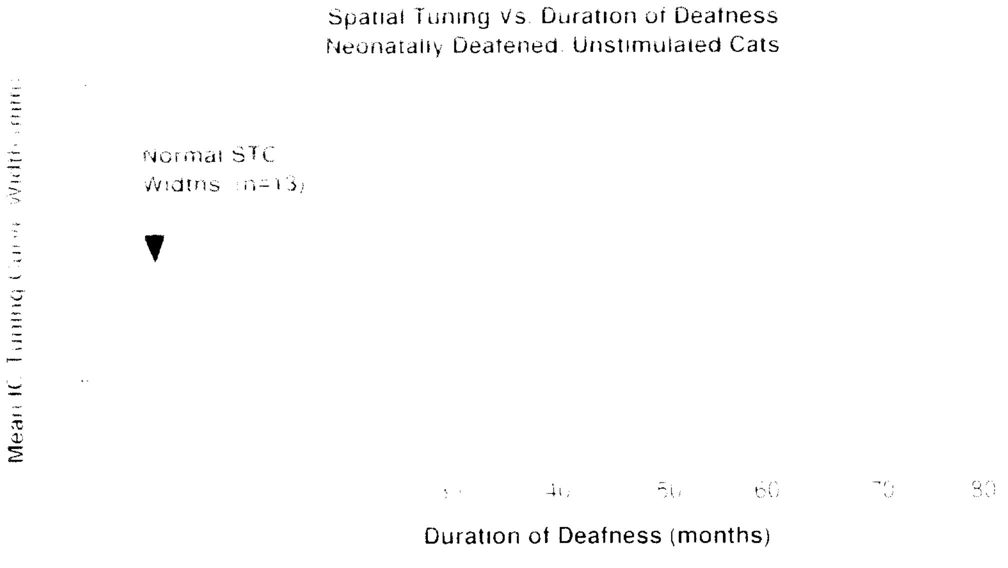


Figure 7. The spatial resolution of neonatally deafened animals examined at up to one year of age was not different from that of the normal animals. The STC width of all of these animals fell below the mean STC width of the normal group. In contrast, the spatial tuning of older, neonatally deafened animals [illegible] degeneration is clearly broader.

[illegible] thresholds over time were also compared and are summarized in [illegible] that the mean threshold values for [illegible] MBK and IC [illegible] the neonatally deafened animals [illegible] lower than those values for the [illegible] not significant. As seen in the spatial tuning data [illegible] between the [illegible] MBK response thresholds [illegible] and both the normal group and the [illegible] There is no significant difference between the mean [illegible] group.

Table 11 [illegible] Comparison of Threshold by Group				Pair 1,2	
		Mean Threshold	Normal	Deaf [illegible]	Deaf [illegible]
	Normal	208uAmps±89.7	-	-	-
[illegible]	[illegible]	300uAmps±110	p=0.[illegible]		
	[illegible]	248uAmps±113	p=0.42	[illegible]	-
	Normal	16[illegible].5uAmps±30.4	-	-	-
[illegible]	[illegible]	29[illegible].5uAmps±48.4	p=0.20	-	-
	[illegible]	[illegible]uAmps±89	p=0.31	p=0.08	-

Comparison of Electrode Carrier Location The experimental data reported [illegible] the neural activation resulting from the stimulation of apical electrode [illegible] basal contact in the longitudinal configuration within the three [illegible]. In most of these animals the cochleas were removed and processed for [illegible] examination following the physiology experiment. Dissection of the [illegible] visualization and accurate identification of the stimulating electrode [illegible] cases the tip of the electrode filled the scala tympani, often causing mild [illegible] trauma in the area of the stimulating contact pair (1,2). In contrast, the basal contact region of the electrode (contacts 3 and 4) fills approximately [illegible] scala tympani volume. The location of the electrode carrier within this [illegible] variable. To evaluate the effect of this variability we compared the data from the apical offset electrode pair (1,2) and the basal offset pair (3,4) in both the normal and neonatally deafened animals. These data are summarized in Table 12.

Significant differences in IC responses generated by the apical and basal contact sites were seen for both threshold and spatial tuning in the normal animals. However, neither parameter was significantly different in the chronically deafened animals.

Table 12 [illegible] Electrode Carrier Location
[illegible] IC Responses: Paired Comparisons

		Normal	Long Deafened
[illegible]	[illegible]	[illegible] µAmps	[illegible] µAmps
	[illegible] 3-4	[illegible] µAmps	[illegible] µAmps
	Significance	p=.006	[illegible]
[illegible]	[illegible] 1-2	0.87 mm	[illegible]
	Pair 3-4	1.24 mm	[illegible]
	Significance	p=.05	[illegible]

Summary

[illegible] thresholds for monopolar stimulation are consistently lower than [illegible] configurations. In this study the threshold difference [illegible] was [illegible] both normal and long deafened groups of animals. The difference [illegible] deafened animals was not statistically significant. However, this may [illegible] smaller number of animals available in this group.

[illegible] threshold measurements for different electrode combinations were [illegible]. We found that varying the longitudinal separation of bipolar [illegible] from radial (no separation) to 1.0 mm separation to 4.0 mm separation [illegible] significant effect on the IC response threshold in normal animals. We [illegible] reported the same result for EABR thresholds in a smaller group of [illegible] (QPR #5, Neuroprosthesis Contract # NS-7-2391). It has been argued that [illegible] decrease with increasing electrode spacing because a greater number of [illegible] be present within the field boundaries of the two stimulating contacts and [illegible] separate subset of neurons would be activated with each alternate phase of [illegible] at each end of the alternating polarity stimulus field. Conversely, it [illegible] field intensity or current density gradient decreases rapidly as the [illegible] increases. This decrease in current density would produce higher thresholds. [illegible] similarity of the mean thresholds for these three bipolar configurations [illegible] and 4.0 mm separation) across this study may indicate that these processes [illegible] and that both are important in determining the threshold to a given electrode configuration.

[illegible] mean threshold difference between radial bipolar and offset radial configurations seen in the long deafened animals may indicate differences in anatomy and/or physiology specific to this group. Anatomically, the long deafened animals differ from normal animals by the absence of almost all fibers peripheral to the spiral ganglion, reduced spiral ganglion cell numbers (mean % of normal ganglion cell density = 11.8%) and by higher electrical conductivity both through the habenula perforata and within Rosenthal's canal due to increased interstitial volume and decreased nonconductive myelin. In the case of long deafened animals, with minimal nerve survival, the two mechanisms described above may not be balanced in the same manner as in the normal group. In the chronically deaf animals the spatially restricted, high density field of the [illegible] require greater current before a sufficient number of the [illegible] are [illegible] activated to produce a detectable threshold.

[illegible] found that spatial tuning for monopolar stimulation [illegible] bipolar stimulation [illegible] when the contact separation of [illegible]. This difference in spatial selectivity between monopolar and bipolar [illegible] was statistically significant for both groups of animals.

[illegible] clinical cochlear implant patients varies and cannot be assessed [illegible], it is appropriate to attempt to relate these data to future [illegible]. The data for all animals indicate that significant variation occurs [illegible] spatial tuning as a function of electrode configuration, particularly [illegible] of device and animal groups.

[illegible] used the offset bipolar configuration (pair 1-2) as the baseline for [illegible] stimulating combinations. Monopolar stimulation resulted in [illegible] current levels (a desirable characteristic) but this activation occurred over [illegible] and the cochlea (an undesirable characteristic). Thus reduced [illegible] trade-off against less selective activation with this type of stimulation. [illegible] configuration had a significantly higher threshold in the chronically deaf [illegible] in spatial tuning in either group. The widely separated [illegible] demonstrated very broad tuning in the longest deafened [illegible] significant gain in efficiency in any group. Thus, in terms of optimum [illegible] greatest overall efficiency the offset radial pairing produced the best [illegible] should be noted that significant individual variation was observed in the [illegible] animals. In some individuals monopolar stimulation produced [illegible] tuning, even narrower than that seen with bipolar stimuli. In some [illegible] radial pairing produced very low thresholds. These outlying [illegible] illustrate the advantage of an electrode design which can be customized to [illegible] needs of each patient. However, it is important to note that this capability to [illegible] must not only be designed into the system but must also be [illegible] the clinical fitting protocols for each patient. A versatile, complex device design [illegible] applied in a single, simple strategy will not benefit these unique patients.

[illegible] implications of several additional conclusions from this study are significant in terms of future modelling of electrical stimulation in the cochlear and in theoretical analyses of auditory system function.

Of particular interest was the maintenance of spatial tuning in the neonatally deafened animals studied at less than one year of of age and of two older animals (K26 at 14 months and K24 at [illegible] months). All of these animals demonstrated tuning that was, in fact, more restricted than the average tuning for the normal group of animals (see Figure 7). Subsequent histologic examination of four of these six animals demonstrated a mean spiral ganglion survival of [illegible] of normal. This observation indicates that relatively few spiral ganglion cells are needed to accurately convey the spatial distribution of electrical signals from the cochlea to the inferior colliculus. Longer term deafened animals, with even fewer surviving peripheral neurons, have clearly degraded spatial selectivity. It seems unlikely [illegible] loss of spiral ganglion cells is the primary cause of broadened tuning in these [illegible] mechanisms which might explain this change can be hypothesized [illegible] connections between neurons in the direct pathways leading to [illegible] efferents which may act to limit the spread of activity [illegible] and/or alterations in the balance of neurochemicals which [illegible]

[illegible] tuning in the IC is not accompanied by a significant increase in IC [illegible] the EABR threshold for the long-deafened animals [illegible] was [illegible] than that of either the normal or short term animals [illegible]. The [illegible] threshold for which the synchronized activity of many neurons is [illegible] a detectable voltage may be a function of degraded temporal [illegible] the peripheral neurons in these animals. In this model, individual cells [illegible] normal threshold but at more varied latencies. These responses may [illegible] synchronized to allow detection at low levels. It is also possible that the [illegible] cells in the long deaf animals may generate smaller voltage spikes [illegible] to detect in the far field.

[illegible] position between the apical and basal electrode pairs in this study [illegible] differences in both tuning and threshold in normal animals, but not [illegible] deafened group. While the result in normal animals indicates the [illegible] the positioning of electrodes within the scala tympani the [illegible] deafened animals may indicate that these efforts may be of limited [illegible]. It should be noted however, that an attempt was made in the later [illegible] the long deafened group to move the electrode closer to the [illegible] base of the cochlea. This was done by positioning the basal electrode [illegible] under visual control and gluing the dacron round window cuff in [illegible] to prevent later movement. In several animals this produced basal pair (3,4) [illegible] thresholds (and in some cases IC thresholds) that were comparable to apical pair [illegible]. Thus, the long deafened pair 3,4 threshold and spatial tuning values may [illegible] locations and the 1,2 vs. 3,4 difference in these animals may have been [illegible] this change in technique had not been implemented.

4. The absence of change in both IC and EABR threshold between the normal group and the neonatally deafened group less than one year of age has important implications for the theoretical modelling of intracochlear electrical stimulation and the design of future devices. Current modelling techniques predict that optimum electrode placement would be different for cochleas with and without surviving peripheral dendrites. These two conditions are modelled in the animal populations in this study. We would expect the four animals deafened acutely with intracochlear neomycin and the acutely AOAA deafened adults to have normal (or nearly normal) numbers of peripheral processes extending through the habenula perforata to the organ of corti. In contrast, the neonatally deafened animals, with approximately 75% spiral ganglion cell loss, have very few peripheral neurons. The lack of difference in threshold response between these groups suggests that the spiral ganglion cell body is the probable site of activation for intracochlear electrical stimulation even in the presence of viable dendrites.

[illegible] for the Next Quarter

[illegible] complete the initial series of multiunit [illegible] experiments designed to assess the [illegible] of chronically stimulated animals throughout the term of their stimulation [illegible] will be analyzed and summarized during the next quarter for [illegible] technical report.

[illegible] the collection of EABR data to varied interpulse intervals and [illegible] and action potentials for all stimulated animals.

[illegible] the histologic analysis of two animals which were deafened as adults [illegible] chronically stimulated with amplitude modulated pulse trains. These [illegible] to similar data in neonatally deafened kittens. We will continue [illegible] two other animals in this series.

[illegible] initiated the stimulation of two neonatally deafened animals with higher [illegible] AM stimuli (800pps modulated at 60Hz). Stimulation of these animals will [illegible] the next quarter. Two additional kittens (age [illegible] weeks) will be [illegible] chronically stimulated as a part of this series.