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Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

In several previous studies, we have suggested that chronic electrical stimulation through a cochlear implant causes significant alterations in the central auditory system of neonatally deafened cats (e.g., Snyder et al., 1990, 1991, 1995; Leake et al., 2000, Vollmer et al., 2000). However, the effects of developmental critical periods on these results are unknown. This Quarterly Progress Report presents the results of a study which examined the effects of chronic stimulation on the mature auditory system.

Normal hearing adult animals were deafened using ototoxic drugs (kanamycin and ethacrynic acid) and received daily chronic electrical stimulation through a specially designed cochlear implant. Following 4-6 months of chronic cochlear stimulation the response thresholds to pulsatile and sinusoidal signals were recorded within the inferior colliculus. Using previously established methods, threshold vs IC depth functions called spatial tuning curves (STC) were constructed, and the widths of the curves were measured to infer spatial selectivity of the stimulated electrode pair. These results were then compared with earlier data from neonatally deafened, chronically stimulated animals.

The average STC width in the adult deafened animals (1.1 mm) was significantly broader ($p>.001$) than that seen in control animals (adult/unstimulated animals; 0.74 mm). Moreover, the broader STC observed in adult deafened animals was not significantly different from the neonatally deafened, early stimulated group (1.51mm). The IC spatial representation in the adults was nearly identical for pulsatile and sinusoidal stimulation (0.9 mm vs 1.1 mm) when phase duration was taken into consideration. However, sinusoidal stimulation consistently produced response thresholds at much lower intensities than pulsatile stimulation, a difference that could not be solely attributed to differences in charge/phase.

The results suggest that passive stimulation of the auditory system of mature animals can induce significant plasticity, as evidenced by the spatial expansion of the cochleotopic organization of the inferior colliculus. In addition, although the spatial spread of excitation in the IC appears to be similar for pulsatile and sinusoidal stimulation, differences in neural response thresholds were observed which could not be explained completely by the difference in basic signal properties (charge/phase).

ALTERATIONS IN THE SPATIAL SELECTIVITY OF THE INFERIOR COLLICULUS FOLLOWING CHRONIC ELECTRICAL STIMULATION WITH A COCHLEAR IMPLANT IN ADULT CATS

1. INTRODUCTION

For three decades cochlear implants have been used successfully to restore auditory input to profoundly deaf adults and children who obtain minimal or no benefit from conventional hearing aids. Speech perception performance utilizing these devices has been characterized by wide variability among users. Some individuals display remarkable results and are able to use a conventional telephone almost immediately, whereas others receive only minimal benefit and display poor speech discrimination even after long periods of use. These differences in performance have been attributed to a number of factors including age at deafness onset, duration and etiology of deafness, placement of the intracochlear electrodes and functional integrity of the central auditory system (Nikolopoulos et al., 1999; van Dijk et al., 1999; Tyler et al., 1997).

Prelingually deaf individuals typically demonstrate poorer speech discrimination performance as compared to individuals with onset of deafness during or following the acquisition of speech and language (Osberger et al., 1991; Robinson, 1998). This finding has been attributed to a 'critical period', a developmental period during which auditory input is necessary for the attainment of normal speech and language (Rubens and Rapin, 1980; Eggermont and Bock, 1986), and has served as a rational for early cochlear implantation. Further support for implanting very young children has come from the assumption that the immature nervous system is more malleable (plastic) than the mature auditory system and, therefore, has a greater capacity for adapting and interpreting the highly artificial electrical signals presented by a cochlear implant.

However, significant plasticity also has been observed in mature nervous systems (For review see Kaas, 1997). In fact, adults who are deaf for long periods of time and then receive a cochlear implant often obtain substantial benefit, although significant improvement or a plateau in performance may require a prolonged period of use (Dorman, 1993; Schindler et al., 1995; Gstoettner et al., 1998; Tyler et al., 1997).

While the anatomical consequences of deafness on the developing and mature auditory system are relatively well documented, only limited information is available about the effects of chronic electrical stimulation in deaf subjects. The majority of chronic stimulation studies have described anatomical and functional effects using models of *early* acquired deafness. The results have

demonstrated that chronic intracochlear electrical stimulation can have both beneficial and detrimental effects on the central nervous system. It has been shown that chronic intracochlear electrical stimulation may maintain cellular survival, but it may also cause significant alterations in the central topographic representations of the cochlea. Thus, anatomical studies have suggested that chronic intracochlear electrical stimulation partially delays or prevents deafness-induced degeneration of primary auditory neurons (Loustaeu et al., 1987; Hartshorn et al., 1991; Leake et al., 1991; 1992; 1999). Electrophysiological studies have shown functional changes in the central representation of the chronically stimulated cochlear sector (Snyder et al., 1990, 1991; 1995). Specifically, chronic intracochlear electrical stimulation results in an expansion of spatial representation that has been interpreted as potentially deleterious. On the other hand, chronic stimulation can also result in an increase in the frequency following capabilities of central auditory neurons (Snyder et al., 1995; Vollmer et al., 1999) and an overall increase in the recruitment of auditory cortex (Klinke et al., 1999).

While these findings are significant in the *early*-deafened auditory system, far less is known about the effects of chronic intracochlear electrical stimulation on the mature auditory system. The role of development in mediating these effects has not been determined. Some studies in adult animals have suggested that spiral ganglion degeneration after deafness is ameliorated by chronic stimulation (Lousteau, 1987; Hartshorn et al., 1997; Miller et al., 1997). However, other investigations have failed to demonstrate these effects (Li et al., 1997; Shepherd et al., 1994; Araki et al., 1998). Moreover, studies of the functional consequences of electrical stimulation in inducing plasticity of the adult central auditory system have not been reported.

In addition to the contribution of age at onset of deafness to the intersubject variability observed in performance, differences in the signals and processing strategies implemented by clinical cochlear implant speech processors may also contribute to the variability in performance. Currently available devices use either analog (sinusoidal) or pulsatile signals in their electrical outputs. Some systems are capable of providing just one type of signal, whereas others have more versatility and permit selection of either signal type. It has been suggested that some individuals prefer and/or perform better utilizing one signal type as compared to another (Schindler et al., 1995; Osberger et al., 1999; Battmer et al., 1999; Kompis et al., 1999). However, in a recent study of performance over time, which compared two groups of subjects using devices that delivered either analog or pulsed signals (CIS processor), no significant difference in group performance was found (Tyler et al., 1997).

To examine the influence of chronic intracochlear electrical stimulation and the choice of signal processing strategy in the mature auditory system the physiological responses to intracochlear stimulation were examined in an adult model of deafness. The spatial distribution of excitation thresholds elicited by electrical stimulation of the cochlea within the IC of adult cats after deafening and chronic intracochlear stimulation was determined. These data were then compared to IC data from previously reported studies of control animals and neonatally deafened animals that were chronically stimulated (Snyder et al., 1990**;** Vollmer et al, 1999.; Leake et al., 2000;).

2. METHODS

Experiments were conducted in six healthy adult cats (>2.5 kg) purchased from commercial vendors and housed in the Animal Care Facility at the University of California San Francisco. All experimental procedures were approved by the University's Committee on Animal Research and met the NIH guidelines for the care and use of animals in research.

2.1 Deafening

The cats were sedated initially with an intramuscular injection (IM) of ketamine HCl (33 mg/kg) and acepromazine maleate (0.1 mg). The forearm was shaved and an intravenous (IV) catheter inserted into the cephalic vein. Sedation was maintained with additional injections of ketamine or sodium pentobarbital (25 mg/kg, IV) as required. Baseline acoustic auditory brainstem responses (ABR) were recorded in an intensity series, and normal thresholds (<25 dB SPL) were documented for both ears. Animals were then deafened by co-administration of kanamycin and ethacrynic acid as described by Xu et al. (1993). Briefly, kanamycin (300 mg/kg) dissolved in sterile saline solution was injected subcutaneously. After a delay of 20 minutes, ethacrynic acid dissolved in saline (1 mg/ml) was administered by an infusion pump (Razel, Model A-99) set to inject 1 ml/minute. Drug infusion was continued until no ABR response was obtained to clicks at equipment maximum (110 dB peSPL). The ABR was monitored for 4 hours to ensure that hearing did not recover. All animals were given intravenous or subcutaneous fluids, and a heating blanket maintained body temperatures during recovery from the procedure.

2.2 Cochlear Implantation

Approximately 2 weeks after deafening each animal underwent surgical implantation of the left cochlea with a specially designed UCSF feline scala tympani electrode (Fig. 1). The electrode consisted of four platinum-iridium wires embedded in a silastic carrier. Each wire ended in a ball contact that was 300 μm in diameter. The electrode contacts were numbered 1 through 4 (from apical to basal). Electrode leads were coiled in a percutaneous cable that terminated in a microconnector (See Snyder et al., 1990).

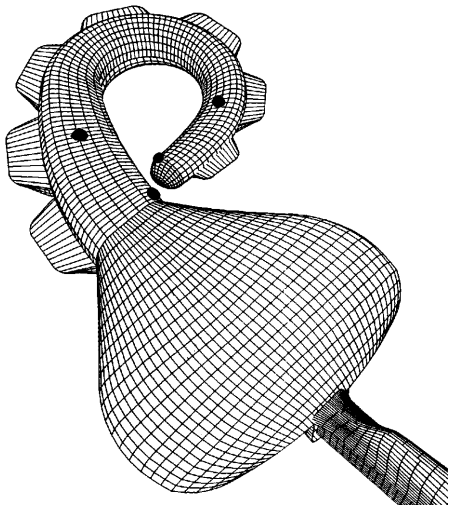

Figure 1. University of California San Francisco feline intracochlear electrode. In this study the apical electrode pair (1,2) was chronically stimulated. Each stimulating contact is 300 mm in diameter. The overall electrode length is 9 mm from the bottom of the wing to the apical tip. The center-to-center distance between electrode contacts within a pair (1 , 2 and 3,4) is 1.0 mm. The distance between electrode contact #2 and #3 is 4.0 mm.

For cochlear implantation, the animals were sedated as described above, and profound bilateral hearing loss was confirmed again by ABR testing. The animal's head was stabilized in a standard mouth bar headholder and the scalp shaved and scrubbed for the sterile surgical procedure. Under asceptic conditions, a curved post-auricular incision was made through the skin. The erector pinna and temporalis muscles were reflected rostrally. The strap muscles were reflected ventrally, and the auditory bulla was exposed and opened to access the round window. The round window membrane was opened, and the intracochlear electrode gently inserted into the scala tympani. The extracochlear portion of the electrode had a small dacron fabric skirt which was fixed to the bone just ventral to the round window with Histocryl™ tissue cement. A second cuff secured the implant to the parietal bone just dorsal to the bulla, and a third cuff was secured near the midline of the skull. The percutaneous connector, that allowed connection to the stimulus, was then routed through a small second incision in the skin at the midline of the neck caudal to the initial incision site. The temporalis muscle was re-

approximated and sutured over the electrode cable. The incision site was lavaged with Nolvasan ™ (1%) or Bacitracin (25,000 units/ml) and closed in anatomical layers. Immediately following implantation, physiological thresholds for electrical stimulation were determined by recording electrically evoked auditory brainstem responses (EABR). Buprenorphine HCl (0.005 mg/kg) was administered for analgesia, along with prophylactic antibiotics, and the animals were allowed to recover with continuous monitoring.

2.3 Evoked Potential Recordings and Signal Generation

Acoustic and electrical auditory brainstem responses were recorded differentially from silver wires inserted through the skin (vertex - active; ipsilateral mastoid - reference; and contralateral - ground), amplified (100,000x) and bandpass filtered (0.01-10.0 kHz), using a battery powered preamplifier (DAM-50) and a plug-in oscilloscope amplifier (3A9 Tektronix). *Acoustic* stimuli (200 μsec clicks, 20/sec) were delivered through a canister headphone (STAX, model SMR-1/MK-2) coupled to the ear by a hollow ear bar inserted into the external ear canal. *Electrical* stimuli consisted of biphasic square wave pulses, 200 μsec/phase, 20 pps delivered to the cochlear implant via a specially designed optically isolated, voltage-to-current amplifier (Vureck et al., 1981). All stimuli were charge balanced (capacitatively coupled). This amplifier was calibrated prior to every recording session to deliver 100 μA output for a 1 volt peak-to-peak input into 10 kΩ resistance. All stimuli were generated by a TMS 3200 PC based workstation driven by custom software. The input to the voltage-to-current amplifier was controlled using an attenuator (Tucker Davis, model PA-4), and the amplifier was calibrated to deliver 100μA output for an input of 1.0 volt. The signal was then delivered to the intracochlear electrodes through a switch box connected by cable to the percutaneous connector. The switch box facilitated delivering electrical stimuli to different pairs of intracochlear electrodes throughout the experiment.

For all evoked potentials (acoustic and electric) responses were averaged for 500-1000 stimuli using a 16-bit A/D converter IBM PC operating at a sampling rate of 30 kHz. Visual detection levels, the lowest intensity level at which a repeatable response was just detectable and confirmed by two observers, were used to determine threshold.

2.4 Chronic Electrical Stimulation

Electrical stimulation was initiated within one week after cochlear implantation. Stimulation periods were 4 hours/day, five days/week, and all animals received stimulation on the most apical electrode pair (1,2). Detailed stimulation histories are presented in **Table 1**. Electrode impedances were recorded daily before and after stimulation.

STIMULATION HISTORIES

Animal Number	Stimulation Period (days/wks)	Stimulation Level (μAmp)	Duration of Deafness (wks.)
158	116/22	100	24
497	133/30	50-126	32
087	144/32	100-251	33
401	105/21	126-200	23
115	198/39	200-501	41
114	167/33	40-158	36

TABLE 1. Stimulation histories and length of deafness and for the 6 adult cats included in this study.

The electrical stimulus consisted of a continuous train of sinusoidally amplitude modulated (SAM) pulses (200 μsec/phase) delivered at 300 pulses/second and 100% amplitude modulated at 30 Hz. The stimulus intensity was adjusted so that the peak current was 2 dB above each individual animal's EABR threshold. EABRs were recorded periodically (at intervals of about one month), and the current level of the stimulus was adjusted as necessary.

2.5 Acute Electrophysiological Experiments

The animals were sedated, and an IV catheter inserted into the cephalic vein. To prevent brain edema, dexamethasone (1mg/kg, SQ) and mannitol (250mg/ml, IV) were administered daily throughout the course of the 48-72 hour experiment. Prophylactic antibiotics were given (cefazolin sodium; 100mg/ml, SQ) twice daily, and atropine sulfate (0.045 mg/kg, SQ) was given as necessary to control secretions. Heart rate, respiration rate, oxygen saturation and body temperature were monitored continuously.

The head and neck were shaved. A tracheostomy was performed and a tracheal tube inserted and sutured in place. The animal's head was stabilized in a standard mouth bar head holder. A lateral craniotomy was made through the right parietal bone just anterior to the tentorium. The dura was

opened and the underlying occipital cortex removed by aspiration to expose the right half of the tentorium and the rostral portion of the right inferior colliculus. A portion of the tentorium was removed allowing direct visualization of the entire dorsolateral surface of the IC.

IC responses were recorded using Paralene-coated tungsten micro-electrodes with impedances of 0.9-2.0 MΩ. Electrodes were oriented in the coronal plane and tilted off the mid-sagittal plane at an angle of 45 degrees from midline. This allowed the recording of neural activity orthogonal to the cochleotopic frequency gradient (Merzenich and Reid, 1974; Snyder et al., 1990; Brown et al., 1997). The recording electrode was held in position by a micromanipulator, and the depth was controlled remotely by a micropositioner (Kopf, Model 650). A second tungsten recording electrode, carefully matched in impedance, was placed in the surrounding neural tissue to serve as a reference electrode for differential recording. The outputs of the electrodes were differentially amplified (DAM-50) 1000x and bandpass filtered (0.1-10.0 kHz). Second stage amplification (100x) (Tektronix 5110) was utilized and the responses visualized on the oscilloscope. A silver wire electrode inserted through the skin at the neck served as a ground.

Single and multi-neuron thresholds were determined at 100 μm intervals along each penetration through the IC for both stimuli (sinusoid and pulsatile) and for different combinations of intracochlear stimulating electrode pairs. Threshold values were plotted as a function of electrode depth in the IC to construct spatial tuning curves (STC) for each IC penetration (see figure 2). Data were 3-point smoothed. Typically, these functions were ‘w’ shaped with two distinct regions of low threshold (minimum threshold) and a high threshold region between them. This high threshold region indicates the border between the two subnuclei of the inferior colliculus, the external (ICE) and the central (ICC) nucleus (Vollmer et al., 1999). The width of each STC within the ICC was measured for specific electrode configurations at 6 dB above the minimum threshold for sinusoidal stimuli. Mean STC widths for sinusoids were calculated in order to compare the spatial selectivity of stimulation to data reported in previous studies of normal and neonatally deafened animals (Snyder et al., 1990; Leake et al., 2000). In addition, since pulse trains were used for chronic stimulation, STCs constructed in response to pulsatile stimuli also were examined. The pulse STC widths were determined at the current levels used for chronic stimulation and at 2 dB above the minimum threshold. These results were used to estimate the relative efficacy and selectivity of activation of the central auditory system during chronic stimulation.

3. RESULTS

3.1 Cochlear locations of stimulating electrodes

Table 2 presents the cochlear positions of the individual intracochlear electrodes determined from cochlear surface preparations. In each cochlea the basilar membrane length was measured, the location of each electrode contact determined, and the represented frequency was estimated using the Greenwood (1974) frequency-position function with the revised constants provided by Liberman (1982).

Basilar membrane length ranged from 22.7 to 25.2 mm with a mean of 24.4 mm. Overall there was relatively little intersubject variability in electrode placement. The average position of the most apical electrode (#1) was 12.6 mm and electrode #2 was 11.6 mm. The bipolar stimulating (apical) electrode pair (1,2), therefore, was centered in the upper basal turn of the cochlea at a location representing about **5.2 kHz.** The average location of the basal electrodes was 7.6 mm for electrode 3 and 6.6 mm for electrode 4, representing frequencies of 13.1 and 15.9 kHz, respectively. Thus, the basal-most electrode pair (3, 4) was 5 mm basal to the apical pair and centered around **14.5 kHz.** Overall, the results suggest that the electrode pairs along the cochlear spiral were positioned similarly across animals. This was an essential requirement for valid comparison of STC data recorded from a given electrode pair in different animals.

Electrode Contact	**1**	**2**	**3**	**4**	**Basilar Membrane**
	Distance from cochlear base (%)				**Length**
Animal Number					**(mm)**
087	12.3 (49)	11.2 (45)	7.1 (28)	6.1 (24)	25.0
497	12.5 (50)	11.5 (46)	7.5 (30)	6.5 (26)	25.0
401	12.1 (48)	11.2 (44)	7.2 (28.5)	6.2 (25)	25.2
158	13.5 (56)	11.5 (48)	7.5 (31)	6.5 (27)	24.1
114	11.5 (51)	10.5 (46)	6.5 (27)	5.5 (24)	22.7
115					
Mean	**12.6 (50.9)**	**11.6 (46.2)**	**7.6 (30.0)**	**6.6 (25.8)**	**24.4 mm**
***Frequency**	**4.51 kHz**	**5.8 kHz**	**13.1 kHz**	**15.9 kHz**	

TABLE 2. Electrode positions along the basilar membrane. The location of the stimulating electrode contacts (#1-4) are given in mm from cochlear base and percent distance along the cochlear spiral. Cochlear length (mm) is shown for all animals. The mean distance from the cochlear base for each electrode contact and the mean estimated frequency (* Greenwood, 1974, Libermann, 1982) represented by each electrode are provided.

3.2 Spatial Selectivity/Acute Electrophysiology

Threshold values obtained at 100 μm intervals were plotted as a function of electrode depth in the IC to construct an STC for each IC penetration. Several complete penetrations (4-6) were made through the IC of each animal, and STC were constructed for different bipolar electrode configurations including pairs (1,2; 3,4 and 1,4) for pulsatile and sinusoidal stimuli. In addition, STC for monopolar electrodes (1M, 2M, 3M, and 4M) activated against a distant ground were generated for sinusoidal stimulation to help define the boundary between the ICE and ICC. For sinusoidal stimulation the plots of threshold for a given electrode pair as a function of depth were 'w' shaped with a high threshold region adjacent on both sides to regions of minimum (low) thresholds. This finding was consistent with previous reports (Vollmer et al**.,** 2000). In contrast, STC to pulsatile signals were higher in threshold and were generally characterized by less distinct low threshold regions than curves for responses to sinusoidal signals.

3.2.1 Bipolar Sinusoidal Stimulation

Figure 2 illustrates exemplary STC for 100 Hz sinusoidal stimuli from 1 penetration in an adult deafened cat. The border between the external and central nucleus is defined by the high threshold region (vertical hatched line). Stimulation delivered to the apical electrode pair 1,2 resulted in an STC with a distinct minimum threshold (20 dB) in the ICC at 3200 μm, whereas, stimulation of the basal (high frequency) electrode pair 3,4 had a minimum ICC threshold (17 dB) at 4100 μm. In nearly all penetrations (23 of 24) in the 6 experimental animals, the apical electrode pair (1,2) elicited excitation at a more superficial region of the ICC than the basal electrode pair (3,4). The mean location (IC depth) for the threshold minimum of electrode pair 1,2 in all cats was 2679 μm, and for electrode pair 3,4 the minimum occurred at 3266 μm. Thus, the average separation of the threshold minima for STC for the apical and basal electrode pairs was 600 μm. These findings indicate that electrical stimulation of the apical, 'low frequency' electrode pair consistently activated a more superficial region of the IC than stimulation of the basal 'high frequency' electrode pair. This systematic representation reflects the well-known tonotopic representation of the ICC with low frequencies being represented more superficially than high frequencies (Snyder, et al., 1990; Leake et al., 2000). Moreover, these mean 'best locations' of 2679 and 3266, when plotted on the frequency gradient across the IC of normal cats (see Snyder et al., 1991), correspond to the 5-6 kHz and 12.0 kHz cochlear regions which are roughly equivalent to estimated intracochlear locations of the stimulating electrode pairs (Table 2).

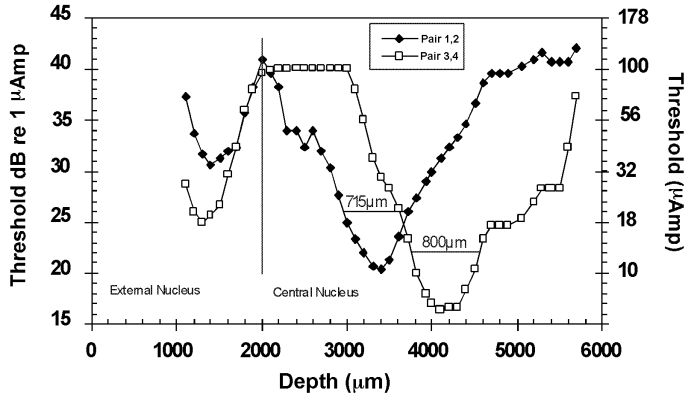

FIGURE 2. Exemplary spatial tuning curves (STC) recorded in the IC of a deaf cat (#401). Response thresholds to 100 Hz sinusoid stimuli are shown for apical (1,2, closed symbols) and basal (3,4, open symbols) stimulating electrode pairs. Minimum threshold for the apical pair was located more superficially than that for the basal electrode pair. STC widths were measured at 6 dB above the minimum threshold (horizontal line in each curve). The vertical line denotes the physiological border between the external and central nucleus of the IC.

The horizontal lines in each curve in Figure 2 represent the width of the curves measured 6 dB above minimum threshold. In this example, the STC width for stimulation of electrode pair 1,2 is 715 μm and for electrode pair 3,4 is 800 μm. The 6 dB widths of STC for all penetrations in each animal are summarized in Table 3. STC widths are provided for electrode pairs 1,2 and 3,4 in all animals except CH115, in which data from electrode pair 3,4 were unavailable due to a broken electrode wire in the cochlear implant. The individual STC widths ranged from a minimum of 420 μm to a maximum of 2000 μm. In individual subjects the 6 dB widths varied from penetration to penetration by as little as 260 μm in #401.3 to as much as 1350 μm in #115**.** The mean 6 dB widths for the individual animals ranged from 613 to 1486 μm. Overall for the group, the mean STC width was 1115 μm for electrode pair 1,2 and 1025 μm for electrode pair 3,4. It should be noted that the average 6 dB width for pair 1,2 was greater than that of pair 3,4 in all but one animal. However, consistent with an earlier report on neonatally deafened and stimulated animals (Snyder et al, 1990), this small difference in STC width between the two electrode pairs was not significant (Student's t-test; $P = 0.37$). Thus, chronic stimulation of electrode pair 1,2 (apical channel) resulted not only in marked expansion of the central representation of the apical stimulated channel, but the basal (unstimulated) pair as well.

Animal #	**158**		**497**		**87**		**401**		**114**		**115**
Electr. Pair	**1,2**	**3,4**	**1,2**	**3,4**	**1,2**	**3,4**	**1,2**	**3,4**	**1,2**	**3,4**	**1,2**
Pen. 1	1800	995	1350	1200	1120	1180	760	620	950	1200	1600
Pen. 2	1400	1360	1260	540	880	1180	620	420	1200	850	750
Pen. 3	1280	1170	1420	1000	540	1160	500	Inc.	1250	1800	650
Pen. 4	1200	900	1000	1180	1100	1310	715	800	1250	Inc.	1550
Pen. 5	1100	930	900	1450	1500	1480			1300	800	2000
Pen. 6									1200	700	
Average	**1486**	**1106**	**1186**	**1074**	**1028**	**1262**	**649**	**613**	**1307**	**1070**	**1138**
Std. Error	**122**	**101**	**100**	**151**	**152**	**60**	**58**	**109**	**123**	**200**	**253**

Table 3. 6 dB widths (microns) for all penetrations in each animal. Widths are given for stimulating electrode pairs (1,2) and (3,4). Avg=Individual averages, S.E.=Standard error, Inc=Incomplete penetration

Figure 3 compares the average STC width of electrode pair 1,2 for all animals in this study with previously published data from our laboratory for acutely deafened control animals and for neonatally deafened, chronically stimulated animals. Adult deafened stimulated animals had significantly broader STC widths than control animals ($P<0.01$). Thus, the mean extent of ICC excited by the chronically stimulated electrode pair was significantly expanded in these subjects.

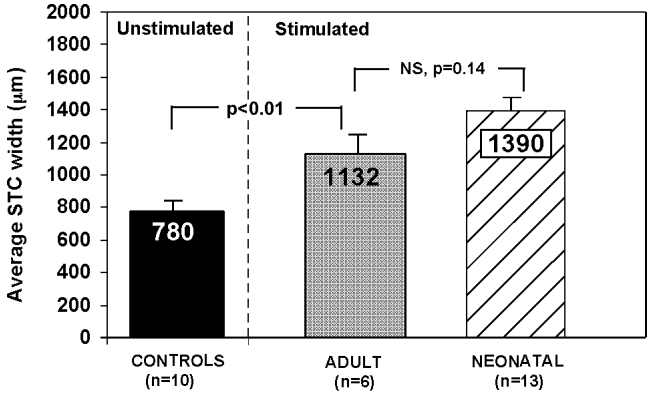

Figure 3. The average 6 dB STC widths (pair 1,2) for the adult deafened animals in this study are compared to the average STC widths previously reported for control, unstimulated animals and for neonatally deafened, chronically stimulated cats (Leake et al., 2000).

As mentioned previously, our prior studies conducted in neonatally deafened animals also have demonstrated significant expansion of the ICC representation of the stimulated channel. Figure 3 shows the mean STC width (1.4 mm) for neonatally deafened subjects (n=13) that were stimulated for several months using electrode pair 1,2 (using protocols similar to the present study) as reported

previously (Leake et al., 2000). This value represents a 1.5 times increase compared to normal controls (n=10). It is interesting to note that this mean STC width for the neonatally deafened group was somewhat higher than that recorded in the adult deafened experimental group (1.1 mm). However, this difference did not achieve statistical significance (*P*= 0.14), suggesting that both animal models demonstrated similar spatial expansions as compared to the control group.

In the present study, the mean absolute minimum thresholds were 24.2 dB for electrode pair 1,2 and 28 dB for stimulation of electrode pair 3,4. Although the average threshold recorded from pair 1,2 was typically slightly higher than pair 3,4, this difference was not significant (*P*=0.10). Further, as illustrated in Figure 4, there was only a weak correlation (r=0.3) between the STC width and minimum threshold. This finding suggests a slight increase in STC width with increasing threshold.

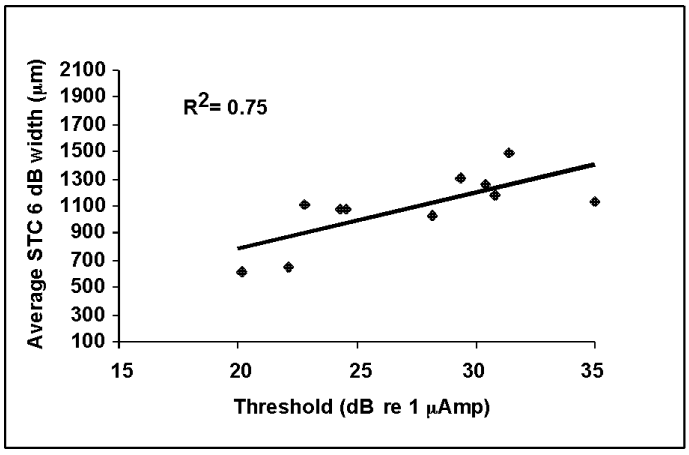

Figure 4. The average STC width (electrode pairs 1,2 and 3,4) vs. average minimum threshold for all animals. Pearson product moment correlation = 0.745

3.2.2 Monopolar Stimulation

Figure 5 compares examples of tuning curves generated in the same penetration for monopolar (a) and bipolar (b) sinusoidal stimulation. By comparison to monopolar stimulation, the bipolar configuration (Fig 5b) shows more distinct areas of excitation near minimum threshold, although there is considerable overlap at higher threshold locations. The monopolar (M) stimulation shows largely overlapping areas of excitation for the apical (1 and 2) and basal (3 and 4) electrodes. Stimulation of 1M and 2M produces minimum thresholds at similar depths, and these two electrodes have nearly identical 6 dB widths suggesting that they stimulate similar neural populations. Similarly, 3M and 4M have locations of minimum threshold at similar depths and nearly identical widths. In this particular example, the results suggest that the more basal electrodes (3M and 4M) stimulate neural populations that have marked overlap with, and essentially comprise a subset of the population stimulated by apical monopolar electrodes 1M and 2M.

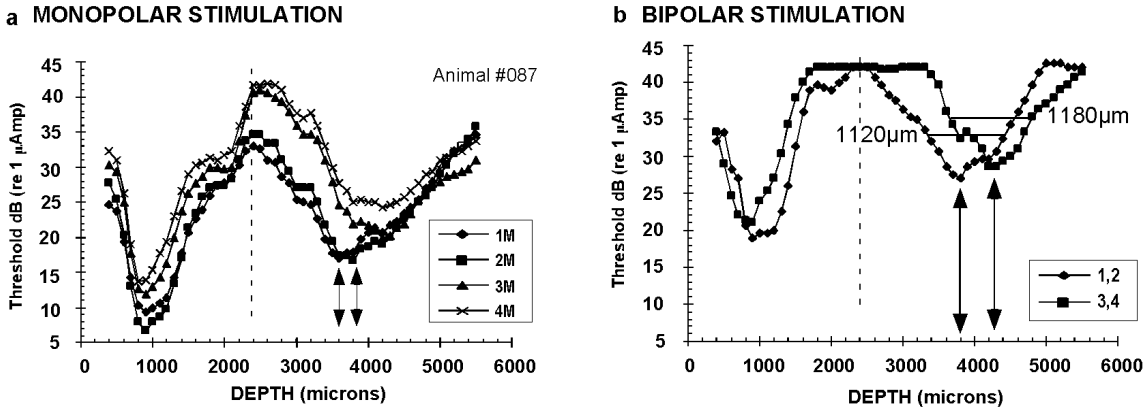

Figure 5. Spatial tuning curves for sinusoidal stimuli presented with monopolar (a) and bipolar (b) electrode configurations. Vertical lines denote the border between external and central nucleus. Arrows indicate the location of minimum threshold within the central nucleus.

Monopolar stimulation produced tuning curves with considerable variability among the four intracochlear electrodes and more variability than bipolar stimulation. Thresholds, tuning curve shape and spatial selectivity all varied widely within and among animals. However, STCs generated from monopolar stimulation in many cases provided valuable information for defining and confirming the border between the external and central nucleus. STCs for monopolar stimulation had minimum threshold that averaged 6.5 dB lower and 6-dB widths that were 10% broader than STCs for bipolar stimulation.

3.2.3. Pulsatile Stimulation

In order to estimate the ICC area activated during chronic electrical stimulation, spatial tuning curves were constructed in response to 0.2 ms/phase *pulses* presented to electrode pair 1,2. In general, pulsatile thresholds were higher and therefore when plotted on the more compressed dB scale the curves appear relatively flat as compared to the spatial tuning curves that are constructed for the sinusoidal data.

Figure 6 illustrates the similarity between 3 electrode penetrations for *pulsatile* stimulation of the apical electrode pair (1,2) in animal #401. Each penetration shows the border between the external and central nucleus clearly evident at approximately 1600 microns. The morphology of the 3 STC was similar, although the absolute threshold for one of the penetrations varied from the others. The first two penetrations had identical response minima at approximately 50 dB, whereas penetration 3 had a minimum that was 10 dB lower. The horizontal dashed line indicates the level of daily chronic stimulation level. Examination of the area of central IC activated for this animal, suggests that during daily chronic stimulation an average of 717 μm of the central IC was activated.

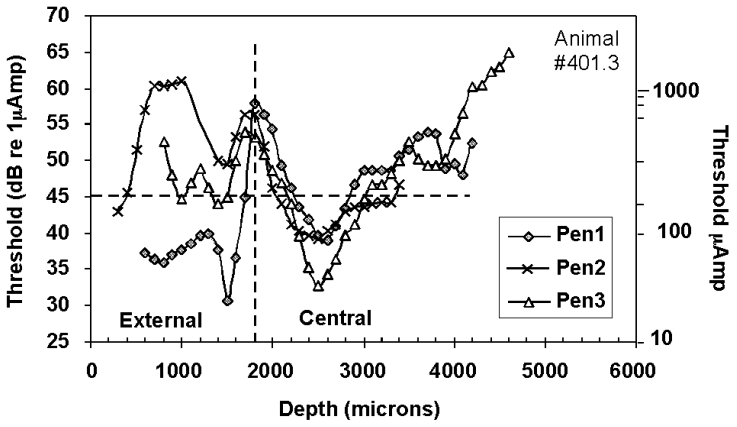

Figure 6. Comparison of spatial tuning curves for pulsatile stimulation of electrode pair 1,2 in three IC penetrations in one cat 401.3. In this example the border between the external and central nucleus (vertical interrupted line) is the same for the 3 penetrations. Horizontal line indicates the level of chronic stimulation.

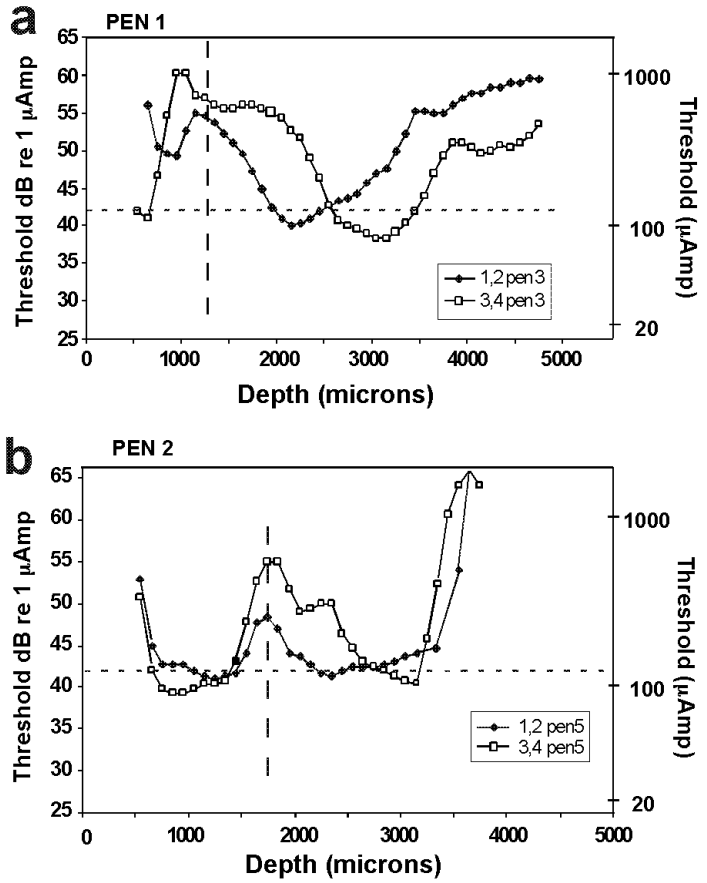

Figure 7. Response thresholds to bipolar pulses plotted as a function of IC depth for 2 different penetrations (a, b) from animal #497. Dashed horizontal line denotes daily chronic electrical stimulation level. The vertical lines show the border between external and central nucleus.

In contrast to the similarity of the within-animal STC shown in figure 6, Figure 7 illustrates the result in an animal in which there was marked variability. This was more commonly observed with pulsed electrical signals than with sinusoidal stimuli. In these examples response, thresholds are plotted as a function of IC depth for bipolar stimulation of both pairs 1,2 and 3,4 in two different electrode penetrations. The horizontal dashed lines indicate the daily chronic stimulation level for this animal. In Figure 7a, electrode pair 1,2 has a response minimum at a much more superficial region of the IC than electrode pair 3,4, reflecting the normal frequency organization of the ICC as described previously. These functions suggest that electrode pairs 1,2 and 3,4 stimulate completely distinct, although fairly broad populations of neurons at 2 dB above minimum threshold. In addition, they are quite similar in configuration to STCs for sinusoidal stimulation except for their higher thresholds. In contrast, the curves in Figure 7b have quite different overall shapes, although the apical (1,2) and basal (3,4) channels stimulate different regions of the IC. In this function, stimulation at 2 dB above the EABR threshold (42 dB) for pair 1,2 would activate neurons located about 2200-2300, a distinctly different population of neurons, widely separated from the region activated by electrode pair 3,4

(2800-3100 μm). Moreover, there are differences in the response thresholds between the two penetrations, with somewhat lower thresholds observed in penetration 1 (Fig. 7a), particularly for electrode pair 3,4. Finally, in these examples, the border between the central and external nucleus occurs at a substantially different location in the two spenetrations.

Table 4 presents summary data for pulse STC widths measured in all penetrations of all the subjects. Widths were measured at the level of daily chronic intracochlear stimulation and at 2 dB above the best (minimum) STC threshold. Measurements at the level of chronic stimulation were taken to infer the area of IC stimulated with the pulsed electrical signal. The pulse STC widths were measured at 2dB above the best minimum level, rather than the 6-dB level used for sinusoidal signals, in order to correct for the much shorter phase duration of the pulses (i.e., 200 μsec/phase pulses vs. 5.0 ms/phase for 100 Hz sinusoids). Incomplete penetrations and penetrations in which the border between the external and central nucleus could not be determined were excluded from analysis. The average STC widths at the level of stimulation ranged from 413 to 1440 μm with an overall mean of 919 μm. STC Width measurements at 2dB above the minimum threshold produced essentially the same overall average (907 μm). However in half of the animals the area of the IC driven at chronic stimulation level was substantially broader that the width measured at 2 dB above STC minima, whereas in the other subjects the opposite was true. Thus the correspondence between the chronic stimulation levels (which were set re: EABR threshold) and the 2 dB pulse STC widths measured at the final physiology experiment was quite variable across subjects. These finding suggests a substantial difference among the animals in the area (amount) of IC stimulated during daily chronic stimulation.

Animal Number	**158**	**497**	**087**	**401.3**	**114**	**115**	**Average**
2 dB above STC Min.	630	581	1890	425	938	980	**907**
Stimulation Level	450	413	1100	750	1363	1440	**919**

Table 4. Average pulse STC widths (microns) for electrode pair 1,2 measured at 2dB above the spatial tuning curve threshold minima and at the level of final stimulation (EABR+2 dB).

3.2.4. Threshold: IC vs. EABR

Minimum IC thresholds are plotted as a function of EABR thresholds for individual animals in Figure 8. IC thresholds were on the average 3.1 dB lower than EABR thresholds. The fairly high Pearson product moment correlation ($r^2 = 0.64$), suggests that the EABR co-varies with minimum single unit IC threshold. The finding that IC threshold is lower on average than EABR threshold is not surprising and has been demonstrated previously (Beitel et al., 2000; Vollmer et al., 2000). The far-field recorded EABR is the averaged/synchronized and summed response of hundreds, if not thousands of neurons, whereas, the IC threshold data was obtained from single or small numbers of neurons using the most optimum near-field recording technique.

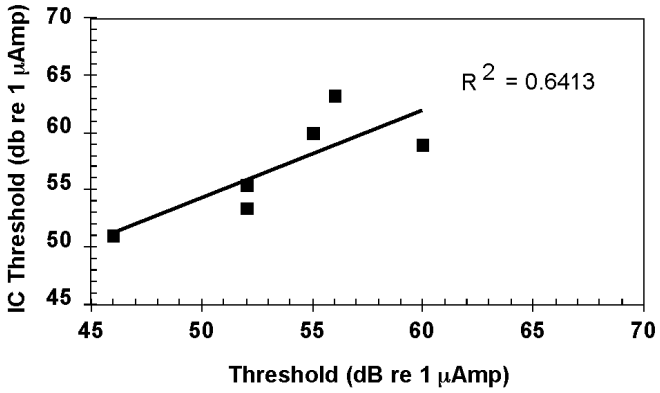

Figure 8. Comparison of the electrically evoked auditory brainstem response (EABR) threshold and IC threshold to pulses for 6 experimental animals. The Pearson product moment correlation value was $r^2 = 0.64$. An isointensity line is shown for comparison.

This result and the previous pulse STC data indicate that chronic stimulation at 2 dB above the EABR threshold is an appropriate method for setting processors at levels that produce effective and relatively selective activation of the auditory nerve.

3.2.5. Comparison of pulse vs. sinusoid data

The physiological responses of IC neurons to sinusoids and pulses revealed a number of differences. First, on the average, neural thresholds to pulsatile stimuli were elicited at an average of 13.1 dB higher than sinusoidal stimuli (range 10dB to –16dB). This is consistent with the fact that 3

cycles of a 100 Hz sinusoid has a 5 ms/phase duration which is approximately 25 times that of the 200 μsec/phase pulsatile signal (see Discussion section 4.6). The longer phase duration results in greater energy within the electrical signal and thus a lower threshold compared to shorter phase duration signals. However, the expected difference based on the different phase duration and waveforms of the 2 signals (pulses vs. sines) used in this study was 25 dB. It is unclear why substantially smaller difference (maximum of 16 dB) was actually observed.

Second, the difference between the two signals was slightly greater at best location. At best location, sinusoidal stimulation elicited responses that averaged 16 dB lower than pulsatile signals (Figure 9).

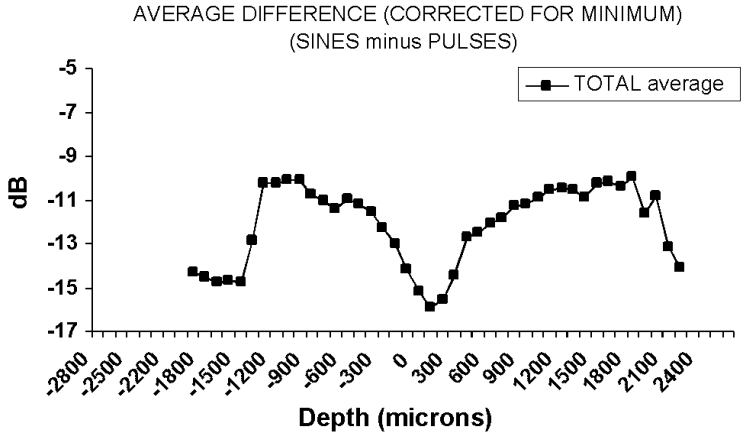

Figure 9. Average difference in threshold (sine minus pulse) across the depth of the IC for all animals in this study. All functions have been adjusted to align the best threshold location (0). The average difference was 13.1 dB. The mean difference at the IC depth of minimum threshold was 16 dB.

The STC width data suggest that the differences in STCs for sines and pulses are not simply attributable to the different phase durations of the two signals, since the STC width results of this study suggest that peripheral stimulation with either sinusoidal or pulsatile stimuli can produce fairly restricted activation of the IC, depending upon intensity. The plotting of the pulsatile signals on the highly compressed decibel scale gives the impression that the IC responses to pulsatile signals are fairly uniformly spread across a large portion of the IC (Fig. 10). However, when taking into consideration the differences in charge/phase of the signals, the results suggest similar STC widths for the two stimuli (Fig. 11). Measurements for sinusoidal stimuli were taken at 6 dB above threshold, whereas STC for pulses were measured at 2 dB above threshold. However, given the difference in threshold, the average sinusoidal and pulsatile threshold the measurements actually were taken at approximately 100 μAmp above threshold for either stimulus condition.

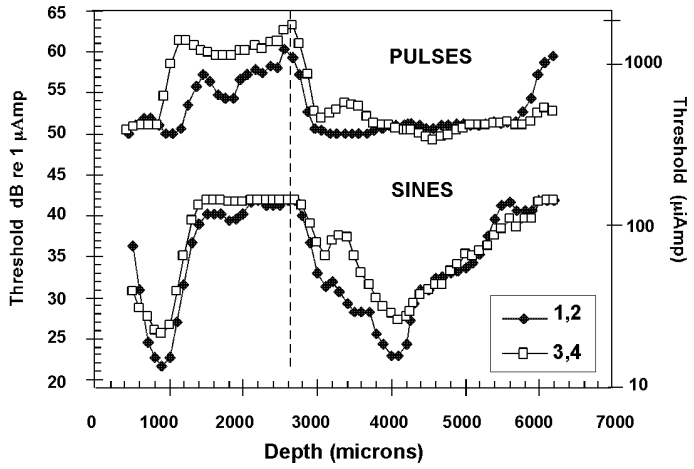

Figure 10. Comparison of STCs plotted for sinusoidal and pulsatile stimuli presented on the two different electrode pairs in animal #087. This graph illustrates the characteristic differences between thresholds for sinusoidal and pulsatile stimuli. Consistent with the differences in the signal phase durations, sinusoidal stimulation has consistently lower thresholds than pulsatile stimuli. Three cycles of a 100 Hz sinusoid has a 5 ms/phase duration which is about 25 times that of the 200 msec/phase pulse stimuli.

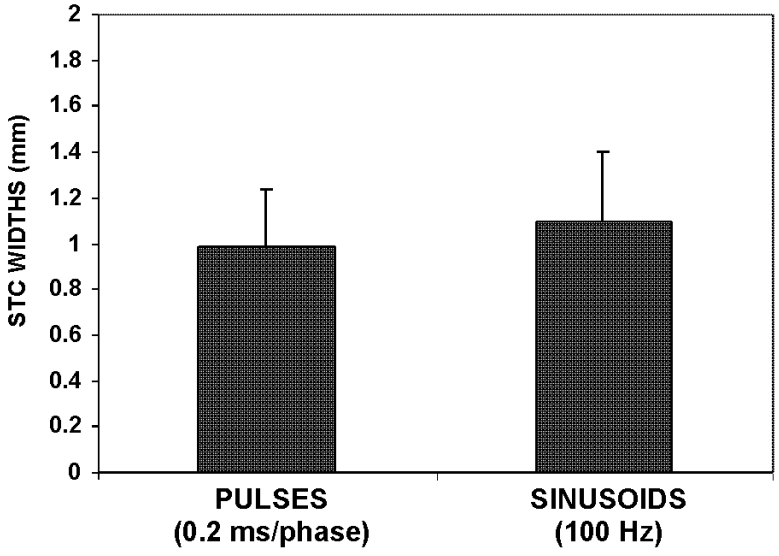

Figure 11. The mean widths of STC for pulsatile and sinusoidal stimuli. The difference in STC width between the two signals was *not significant*. STC widths were determined at 2 dB and 6 dB above threshold for pulsatile and sinusoidal stimuli respectively to partially compensate for signal duration differences and to estimate the region of the IC activated with chronic daily stimulation at 2 dB above EABR threshold..

4.0 DISCUSSION

This study evaluated the consequences of chronic electrical stimulation on the tonotopic organization of the central auditory system in an animal model of adult onset deafness. In previous studies from this laboratory the tonotopic organization and the temporal patterns of single unit responses evoked by intracochlear electrical stimulation have been studied within the auditory midbrain of *neonatally* deafened cats (Snyder et al., 1990, 1991, 1995; Leake et al., 2000; Vollmer et al., 2000). These studies demonstrated the reliability and validity of the electrical STC as a quantitative measure for comparing the selectivity of cochlear stimulation between electrode pairs and animal groups (Snyder et al., 1995; Leake et al., 2000) and described the effects of chronic electrical stimulation on animals deafened from birth. Since these studies evaluated only neonatally deafened, chronically stimulated animals the effect(s) of developmental critical periods on the results were unknown. In the present study, normal hearing adult animals were deafened and chronically stimulation through a cochlear implant to eliminate the potential effects of development on the results obtained.

The cat was selected for study since much of the available data on the encoding of acoustic signals and the effects of electrical stimulation on the peripheral and central auditory system has been documented for this species. Ototoxic drugs were administered to produce a complete, profound sensorineural hearing loss thereby diminishing the likelihood of electrophonic excitation of the auditory nerve by remaining hair cells. Animals were chronically stimulated with a 300 pps electrical signal, amplitude modulated at 30 Hz, a signal which has been shown in neonatally deafened animals to alter the temporal (Snyder et al., 1995; Vollmer et al., 1999) and spatial resolution in neonatally deafened cats (Leake et. al., 2000). The auditory midbrain (inferior colliculus) was selected for physiological study since its cochleotopic organization has been described in detail in response to both acoustical and electrical stimulation (Merzenich and Reid, 1974; Black et al., 1983; Snyder et al, 1990) and this precise organization of the IC allows the inference of relative frequency and selectivity of electrical stimuli in the deaf animal.

4.2 IC Tonotopic Organization

This study was consistent with previous studies in that the cochleotopic location of stimulation corresponded to the known tonotopic organization of the inferior colliculus. Stimulation of the most apical (low cochlear frequency) electrode elicited the best response from deeper regions of the inferior colliculus and stimulation of the most basal channel elicited responses from more superficial locations.

Spatial tuning curves (threshold versus depth functions), in response to sinusoidal stimuli presented to a basal or apical electrode pair, displayed 'W'-shaped curves in which two best locations (minimum thresholds) usually were evident, one in the external nucleus and the other at depths corresponding to the central IC. The high threshold region between these minima delineated the physiological border between the two subnuclei. The depth of the second tip minimum or best location of the curve varied depending on the cochlear position of the stimulating electrode pair (1,2 or 3,4) and corresponded to the known cochleotopic organization of the ICC. The offset of response minima and the non-overlapping parts of the curves observed in STCs of electrode pairs (1,2 and 3,4) suggested excitation of relatively distinct regions of the IC for the different stimulating pairs (see Fig. 2). These STC findings are comparable to studies of control (normal) and neonatally deafened animals (Snyder et al., 1990, 1991; Leake et al., 1999).

In general, the area of IC excited expanded as the intensity of cochlear stimulation increased. At best threshold (response minima) the area of the IC excited with cochlear stimulation was relatively restricted, whereas at higher intensities (suprathreshold) the area of IC excited by stimulation generally increased and many times overlapped that of an adjacent stimulation site. It has been suggested that non-overlapping IC responses from stimulation of 2 cochlear implant channels infers distinct, distinguishable central representations (Leake et al., 2000). Further, human psychophysical studies of electrode discrimination and loudness have revealed that very minimal deterioration in speech discrimination occurs with decreasing intensity, thus changes in the peak or edge of the pattern of excitation may be the important cue for discrimination (McKay et al., 1999).

4.3 STC Expansion in the IC of Adult Deafened Animals

The results suggested that the cochleotopic organization of the IC undergoes significant alteration following a period of chronic intracochlear stimulation of a single channel of a cochlear implant in the adult deafened cat. The mean STC measured at 6 dB above minimum threshold was one and a half times greater (STC width = 1.1 mm) than that recorded for unstimulated control animals (0.74 mm, Snyder et al., 1990; 0.78 mm, Leake et al., 2000) (See Fig. 3). Further, although the STC width was expanded as compared to normal (control animals), it was not significantly different from the average STC width reported for neonatally deafened and chronically stimulated animals (1.51 mm, Snyder et al., 1990; 1.41 mm, Leake et al., 2000). These results suggest that despite a lifetime of normal hearing, the auditory system was capable of significant alteration in response to the chronic electrical stimulation of the auditory nerve. These findings are consistent with studies of the somatosensory and motor nervous systems, which have shown that the adult brainstem and cortex are capable of significant neuroplasticity following peripheral modifications (e.g. Xu and Wall et al., 1999; Bütefisch et al., 2000).

It should be noted that although a significant difference between neonatally deafened and adult deafened chronically stimulated animals was not demonstrated in this study, the average extent of spatial expansion induced in adults was not quite as large as that observed for neonatally deafened chronically stimulated animals. It is thus possible that the methodologies used in this study were not sufficiently sensitive to demonstrate more subtle influences on spatial expansion resulting from the age at onset of deafness and/or differences in the plasticity of the central nervous systems representation of the cochlea between the neonatally deafened and adult deafened animals.

4.4 STC expansion: Mechanisms

A number of studies have demonstrated significant central alterations in response to synchronized neural activation in mature animals (Kilgard and Merzenich, 1998; Recanzone et al., 1990; Nudo, 1990; Stryker et al., 1989) and in humans (Classen et al., 1998; Bütefisch et al., 2000). At least two possible mechanisms for the malleability observed in the central and peripheral nervous systems have been hypothesized, including the sprouting of axons, changes in the efficiency of already existing connections (long term potentiation) and/or modifications in cellular physiology. Evidence that IC neurons in the adult brain undergo changes in inhibitory transmitters, which alter the physiological neuronal responses, have been described in studies of rats and guinea pigs (Bledsoe et al., 1995, Sato et al., 2000). In addition, Bledsoe et al. (1995) demonstrated that mature animals, deafened for 21 days had an increase in evoked Fos-immunoreactive neurons in the central nucleus of the inferior colliculus (CIC) in response to contralateral cochlear electrical stimulation, in comparison to normal or 1-day deafened animals. These results support the hypothesis that IC neurons are capable of substantial alteration even in adults. Moreover, studies such as those of Rao and colleagues (1999) have shown an increase in the number of synapses in the motor cortex of mature rats undergoing self-stimulation, suggesting that synaptogenesis could potentially alter the efficiency of synapses by increasing the strength of inputs from cortical neurons.

The greater STC width for stimulated adult animals as compared to unstimulated controls observed in this study could be elicited by a similar mechanism(s). The synchronous daily electrical stimulation of the central auditory pathway could activate and reinforce already existing weak synaptic inputs within the ICC. Additionally, axonal sprouting or neural regeneration, which has been observed in both developing and mature animals in response to uncharacteristic visual input (e.g. Darian-Smith et al., 1994), is also a potential altering mechanism of the anatomical and thus functional organization of the auditory midbrain. The resulting physiological changes from either of these possible

mechanisms could then be reflected as an expansion of the ICC area responsive to the stimulated sector of the cochlea.

4.5 Selectivity of electrical stimulation

Consistent with previous reports (Snyder et al., 1991; Leake et al., 2000) there was no significant difference in STC width for the chronically stimulated electrode pair (1,2) and the unstimulated pair (3,4). Although the chronically stimulated electrode pair always had a STC width that was greater than the basal unstimulated pair, the difference did not reach statistical significance. This suggests that although the STC data indicates relatively discrete activation of a limited region of the IC with stimulation of electrode pair 1,2 or 3,4 near threshold, some overlapping populations of auditory nerve fibers must have been chronically activated at a suprathreshold level to induce expansion of the 'unstimulated' cochlear sector. It should be noted that Leake et al. (2000) demonstrated that competing stimulation, that is chronic 2-channel stimulation using both apical and basal bipolar electrode pairs, resulted in much more selective spatial representations. In 5 animals studied after chronic 2-channel stimulation, the sinusoidal STC widths were relatively selective, suggesting that distinct central representations of the two implant channels were maintained. In fact, the STC widths were narrower than animals stimulated on a single channel, and were also as narrow as adult deafened controls. This result suggested that the nervous system was capable of discriminating between the competing inputs from two implant channels and maintaining discrete representations, in contrast to the expansion or over-representation seen in adult animals in the current study in which input was delivered only by a single channel.

The average STC widths in the present study were fairly consistent both between and within animals, and the variance was much less than reported in chronically stimulated neonatally deafened animals **(**Snyder et al., 1991; Leake et al., 2000). A number of variables could contribute to variations in STC widths including differences in electrode tip placement (i.e. proximity to SGCs), cochlear pathology (e.g. bone growth vs. fibrous tissue) and/or other factors affecting current spread and excitation patterns. Duration of deafness could also contribute to differences in STC widths; however, these animals had similar lengths of deafness with an average of 33 weeks (see Table 1). Further, animals 401 and 158, with 23 and 24 weeks of deafness respectively, have the greatest difference in average STC width despite having similar lengths of deafness. Studies of human cochlear implant users have described considerable variability both between and within subjects (Pfingst et al., 1997; Tyler et al., 1997) on measures of speech performance. Tyler et al. (1997) studied patient performance longitudinally and found some individuals were 'stable' between 18 and 30 months, yet others

continued to demonstrate significant improvements on speech discrimination tasks over time. These data may suggest that some individuals are capable of relatively rapid improvement and then plateau, whereas others may continue to improve over time. Similarly, in this animal study, alterations in spatial representation may be changing over time with individual animals having potentially different time courses, and neonatally deafened animals, in particular, subject to greater variability due to a more profound impact of the specific attributes of the chronic stimulation..

Finally, variations in STC morphology and widths within an animal, such as that noted for animals #115 (see Table 3) may be due to variations in the trajectory of the recording electrode with respect to the tonotopic organization of the IC. Although the actual angle of trajectory was held constant throughout the course of an experiment, differences in electrode tracts with respect to the borders of the IC (medial to lateral/posterior to anterior) could result in deviations in the orderly frequency representation within the trajectory with respect to the 'isofrequency' laminae. Overall, the STCs displayed good resolution of the border between the ICX and ICC and the separation between the apical and basal cochlear stimulating electrode pairs.

4.6 Pulsatile vs. Sinusoidal Signals

An additional goal of this study was to examine the differences in neuronal response for two different signals, a 0.2 ms/phase pulse and a 100 Hz sinusoid. On average a 0.2 ms/phase pulse required 13.1 dB more intensity than sinusoids to elicit a neural response and even more at the most selective location in the IC. The STCs obtained with pulsatile stimulation typically had higher thresholds and less dynamic range than those recorded with sinusoids. However, selectivity as estimated by the STC widths was similar once the difference in charge/phase was taken into consideration. An estimation of the expected dB difference between sines and pulses using a temporal integration function (Green et al., 1957) suggested a difference between a 100 Hz sinusoid (5 ms/phase) and a 0.2 ms/phase pulsatile signal of approximately 26 dB. Utilizing the equal power equation the decibel difference between signals of different phase durations can be predicted by:

$$\text{Equal power (dB)} = 10 \log T1/T2 \qquad (1)$$

(Where T1 is the phase duration of one signal and T2 is the duration of the second.)

The calculation provides only an approximation of the energy required for two signals of unequal duration to be comparable, since the formula does not take into account some of the inherent differences between the two signals (e.g. slower onset of longer duration signal, difference in capacitance of the stimulating electrode to the two signals, potential for greater artifact contamination with shorter more rapid pulse duration signals). The results of our study suggest that the difference between the two signals may not be solely due to differences in total charge/phase. The difference

observed was that a 0.2 ms/ phase duration signal required a current that was 13.1 dB greater than the longer phase duration signal on average, and 16 dB greater at the most responsive location, only a little more than one-half the expected difference. On the other hand, despite this deviation from the expected threshold difference, the insignificant difference between sinusoidal and pulsatile spatial tuning curves widths suggests that the nervous system may treat both signals relatively similarly. At least with respect to the area (amount) of the nervous system that is involved in processing the signal.

Clearly, additional study of stimulus properties and neural responses are necessary. This is especially apparent since current cochlear implant processors utilize both very short duration pulses and analogue signals, a variable which may contribute significantly to patient performance.

5. Conclusions

The results of this experiment indicate that the central auditory system of mature animals is capable of significant plasticity, even following a lifetime of normal auditory experience. Animals deafened and chronically stimulated as adults had a greater area of the IC responsive to the chronically stimulated sector of the cochlea than control animals without stimulation. Further, this expansion of the central representation was nearly 1.5 times that of the normal animal and was comparable to that observed in neonatally deafened chronically stimulated animals.

Arguments for the implantation of very young children have been based on the premise that if intervention occurs prior to, or during the critical period for speech and language development, then some of the profound effects of deafness may be ameliorated. However, animal studies suggest that very profound functional reorganization may exist with chronic electrical stimulation of the developing nervous system. Arguably, it is unknown whether or not these changes are permanent and thereby eliminate future possibilities for alterations or modifications once the nervous system has matured. The finding of this study suggests that the mature nervous system is capable of nearly comparable alteration following chronic stimulation suggesting that plasticity is also an important feature of the mature central auditory system. It is tempting to suggest that central nervous system changes that occur with stimulation of a young deaf child could later be modified, since the adult animals in this study do demonstrate significant plasiticity. However, it is not possible to conclude whether or not these changes that occur during development would be reversible or further modifiable in the adult as demonstrate here in previously normal adult subjects. Future studies are needed to address these issues.

The second finding of this study suggested that neurons within the ICC do not respond in a predictable way to signals of varying phases. Differences observed in response thresholds, dynamic ranges and spatial tuning to two signals (sinusoidal vs. pulsatile) suggested no preference of the nervous system to either signal. Although sinusoidal signals did exhibit lower thresholds, these thresholds were not as low as expected given the charge/phase of the signal. Spatial tuning curve widths were fairly comparable and suggested similar spread of activation across the IC to either signal. The finding that neither signal produced significantly different response patterns may be consistent with the clinical reports that although some individuals prefer one signal or another, this preference cannot be predicted (e.g. length of deafness, discrimination ability etc.).

6. Future Studies

Future studies need to determine the mechanisms responsible for the expansion of spatial selectivity noted in these mature animals. Current neuroanatomical plasticity data suggests that plasticity involves either adjustments in the strength of connections between neurons or the formation of new neural connections. In a future study, the identification and definition of axonal projections and dendritic branching within the central nervous system could be determined using neural tracers. Examination of the differences in neural connections between stimulated and unstimulated animals is essential to the development of optimum interventional strategies that promote central nervous system organization that consequently is beneficial to implant patients for the optimum detection and discrimination of speech and environmental sounds.

In addition, since past studies have demonstrated that the temporal characteristics of the chronic stimulation signal may affect the temporal response properties of IC neurons (Vollmer et al., 2000), the effects of chronic stimulation with different signals should be examined. The potential for improving, maintaining and/or guiding spatial selectivity may depend on the characteristics of the chronic stimulation signal.

An additional area of interest is the reversibility of such induced functional alterations. Once the central auditory system has undergone neuroplastic modifications, can further modification be induced, and if so, are there limits to the degree of alterability? This information has significant implications for the youngest implant recipients who could benefit from improvements in cochlear implant processors throughout their lifetime.

Finally, what influence does learning (training) have on the central selectivity of cochlear input? In studies of the somatosensory and motor systems, learning has been shown to have a substantial influence on the degree of plasticity (For review see Edeline, 1999). For human cochlear implant users a finding such as this would have important implications for optimizing training and/or modification/upgrade of device processor strategies in attempts to attain the best possible central representation of the acoustic signal.

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Work Planned for the Next Quarter

1) We plan to conduct two terminal acute electrophysiological studies during the next quarter on neonatally deafened animals. One subject is from the new GM1 ganglioside series, and the other subject has been behaviorally trained to discriminate amplitude modulated signals.

2) Two additional neonatally deafened animal will continue chronic stimulation over the next quatres. One subject is again form the new GM1 ganglioside/2-channel stimulation series, and the other subject, deafened at one month of age has also been behaviorally trained to discriminate amplitude modulated electrical pulse trains.

3) Five investigators from the laboratory will attend the annual Midwinter Research Meeting of the Association for Research in Otolaryngology. The abstracts of the 3 papers to be presented on Contract work are appended to this Report.