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Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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ABSTRACT

Some of the most interesting and potentially important functional changes induced by chronic electrical stimulation are the differences in the temporal response properties of central auditory neurons. We previously reported that the temporal resolution of neurons in the inferior colliculus, i.e., their capacity to phase lock or follow pulse trains of increasing frequency, is significantly increased following chronic stimulation (Snyder et al., J. Neurophysiol. 1995, 73: 447-467.) A major focus of our current experiments has been to evaluate the consequences of stimulation with higher frequency electrical signals that are designed to be more temporally challenging to the central auditory system.

Subsequent to the previously published work, single unit data have now been collected and analyzed for experiments conducted in 13 additional animals: i) 5 prior normal, adult deafened cats; ii) 1 long term neonatally deafened, unstimulated animal; and ii) 7 neonatally deafened, chronically stimulated cats. This Quarterly Progress Report presents a overall summary of temporal resolution data incorporating these new results into the existing data sets, and includes single unit data from a total of 31 cats. Results indicate a gradient in temporal resolution of IC neurons that varied with stimulation history. Neurons in prior normal animals followed to an average maximum pulse rate of 98 pulses per second (pps). Long term neonatally deafened, unstimulated animals showed somewhat poorer temporal resolution with a mean maximum phase locking capacity of 80 pps (although this difference from normals did not achieve statistical significance). Neonatally deafened, chronically stimulated animals exhibited a highly significant increase in temporal resolution. to an average maximum of 138 pps. Moreover, among the chronically stimulated animals, those that received low frequency stimulation (30 or 80 pps; n=5) showed just a slight increase to an average maximum following frequency of 106 pps. In contrast, animals that were chronically stimulated with higher frequency, temporally complex and in some cases, behaviorally relevant stimuli, showed a dramatic increase in the maximum phase-locking frequency to 157 pps. Thus, we now conclude that the temporal resolution of the central auditory neurons is significantly increased by chronic electrical stimulation, and the magnitude of this effect is dependent upon the specific temporal properties of the chronic stimulation.

In addition to these acute measurements of temporal resolution, two new methods were explored which allow non-invasive assessment of temporal response properties. Both of these methods use evoked potential recording to quantify the ability of the deafened auditory system to respond to electrical pulse trains of different frequencies. The first method entails the recording of electrically evoked ABRs with the systematic variation of the presentation rate of pulse stimuli. Adaptation of the EABR was observed when the interpulse interval decreased below 15-20 msec. Further, frequency transfer functions appear to be different for animals with different deafness and stimulation histories. The second method was initiated with the active collaboration of one of our Contract consultants, Dr. Charley Finley of the Research Triangle Institute. In these studies an inactive intracochlear electrode was used to record the compound action potential (CAP) generated by electrical stimulation of other electrodes in the scala tympani. These studies parallel human studies being conducted at RTI. As in the EABR studies, the temporal resolution the deafened auditory system appears to vary depending upon the stimulation history of the animal. Both of these techniques may make it possible to noninvasively document changes in temporal resolution in chronically stimulated animals over time so that results in deaf animal models can be related to results in humans.

Temporal Resolution of Inferior Colliculus Neurons in Electrically Stimulated Cats

During the past quarter we have completed quantitative analyses of extensive single unit data from recording experiments in the inferior colliculus in several animals not previously reported. Our previously published report on temporal resolution (J. Neurophysiology 1995, 73: 449-467) included data from 18 cats. Analyses of single unit data have now been completed for 13 additional cats, making a total number of 31 animals, comprising three distinct populations. Animals in the first group are raised with normal hearing and are deafened and implanted as adults. We have studied 6 additional cats in this group, making a total of 16 animals in the group overall. We have studied one additional long term deafened cat in the group of animals that are term neonatally deafened and studied as adults at ages 2 - 4$^+$ years (bringing the total to 4 animals in this group). Finally, experiments were conducted in 7 additional neonatally deafened, chronically stimulated cats, making a total of 13 in this group. Table 1 summarizes the histories of these animals. All were implanted with an intracochlear electrode at age 6 -8 weeks and chronically stimulated (4 hours/day, 5 days/week) for periods up to one year. The chronically implanted animals were further divided into two groups based on their stimulation histories. Six of these cats were stimulated with relatively low frequency pulses (200 µsec per phase biphasic pulses, 30 pps or 80 pps). Seven animals were stimulated with higher frequency signals, either a continuous 300Hz pulsatile carrier, amplitude modulated by a 30 Hz sinusoid, or by the output of a single channel analog speech processor. All of the stimulators were driven in a constant current mode, capacitively coupled and connected directly to the intracochlear electrode by a percutaneous cable.

TABLE 1. Summary of Stimulated Animals

Cat #	Age at Surgery	Age at Initial Stimulation	Stim. Current	Stim. Period	Stim. Frequency	Age at Sacrifice
K63	6.5 wks	7.5 wks	40-125 µA	23 wks	30 Hz	31 wks
K66	8 wks	9 wks	50-100 µA	16 wks	30 Hz	26 wks
K76	6.5 wks	9 wks	800-250 µA	12 wks	30 Hz	19 wks
K83	6 wks	10.5 wks	125 µA	21 wks	80 Hz	32 wks
K71*	7 wks	8 wks	400 µA	9 wks	30 Hz	18 wks
K90	6 wks	7.5 wks	315 µA	23 wks	30 Hz/Beh	31 wks
K62	6.5 wks	7.5 wks	50-200 µA	22 wks	SP	30 wks
K86*	6 wks	9 wks	30-160 µA	44 wks	SP/Beh	55 wks
K89*	6.5 wks	10.5 wks	80-100 A	26.5 wks	300/30 Hz	37 wks
K91*	6 wks	6.4 wks	100-400 µA	31.5 wks	300/30 Hz	38.5 wks
K92*	6 wks	6.4 wks	150 µA	23 wks	300/30 Hz	31 wks
K93*	7 wks	8 wks	40-400 µA	36 wks	SP/Beh	44 wks
K94*	7 wks	8 wks	40-500 µA	34 wks	SP/Beh	42 wks

* indicates animals not included in previous reports

Temporal resolution of single units in the inferior colliculus was measured by recording the response of isolated neurons to a series of biphasic pulses (200µsec/phase), as the interpulse interval was varied in steps of 5 or 10 pulses per second (pps). The resulting modulation transfer functions correlated the number of response spikes with the stimulus presentation frequency. The frequency at which the number of spikes was reduced by 50% is defined as the 6 dB cut-off frequency and the rate at which all but the onset response stops is defined as the maximum cut-off frequency. A total of 698 single units were isolated, recorded and analyzed in this way. The average 6 dB and maximum cut-off frequency for each normal and deafened, unstimulated animal studied is shown in Table 2. Table 3 summarizes the cut-off frequencies for chronically stimulated animals as one group and as divided into two groups based on the frequency of the stimulus received.

TABLE 2. Temporal Resolution of Neurons in Cat Inferior Colliculus
Unstimulated Animals

CAT #	History	Mean Cut-Off Frequency (PPS) 6 dB	Maximum
105	Acute Deaf, Normal	65	110
134	"	48	81
168	"	69	114
188	"	22	49
138	"	58	108
228	"	61	83
316	"	62	108
242	"	61	93
257	"	40	70
958	"	87	167
518	"	62	86
523	"	67	134
637	"	51	89
617	"	50	80
AVERAGE		57	98
K24	Neonatally Deaf >2yr	29	60
K16	" " >3.5yr	54	104
K33	" " >4yr	61	97
K73	" " >3yr	46	60
AVERAGE		48	80

TABLE 3. Temporal Resolution of Neurons in Cat Inferior Colliculus
Stimulated Animals

CAT #	Stimulation History	Mean Cut-Off Frequency (PPS) 6 dB	Maximum
K63	30 Hz	66	110
K66	30 Hz	60	104
K76	30 Hz	56	107
K83	80 Hz	58	98
K71	30 Hz	80	110
AVERAGE	LOW FREQ. STIM	64	106
K90	30 Hz; Beh	84	190
K62	SP	51	139
K86	SP/Beh	93	200
K89	30/300 Hz	73	164
K91	30/300 Hz	72	145
K92	30/300 Hz	66	134
K93	SP/Beh	89	149
K94	SP/ Beh	76	138
AVERAGE	HIGH FREQ. STIM	76	157
AVERAGE	ALL STIM. CATS	71	138

Figure 1 compares the temporal resolution of normal, neonatally deafened unstimulated and chronically stimulated animals. The long deafened (average 3.1 years) animals that had not received chronic stimulation demonstrated the lowest capacity to respond to rapidly presented pulse trains while the chronically stimulated animals were clearly faster than either of the unstimulated groups. Figure 2 refines this comparison by dividing the stimulated group of animals into those which were stimulated with low frequency signals and those which received higher frequency stimuli. With this comparison it is clear that the difference observed between the stimulated group and the unstimulated animals in Figure 1 is attributable to responses from the cats that were chronically stimulated with higher frequency inputs.

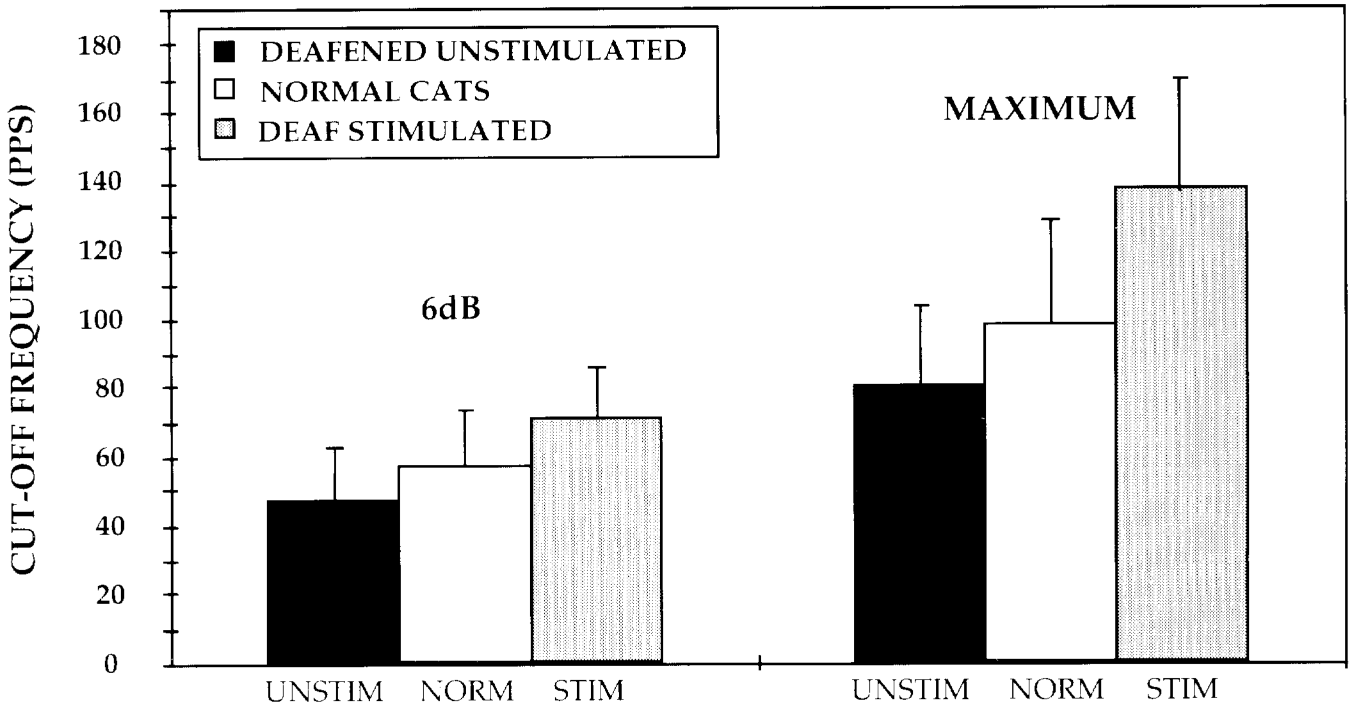

Figure 1. The average 6dB and maximum cut-off frequencies for 698 units from 31 animals are summarized above. As detailed in Tables 1 and 2 these data represent measurements from four neonatally deafened, unstimulated animals with an average age of 3.1 years, fourteen prior normal animals that were acutely deafened less than thirty days before the physiologic experiment and thirteen animals that were neonatally deafened, chronically implanted and stimulated five days per week for up to one year.

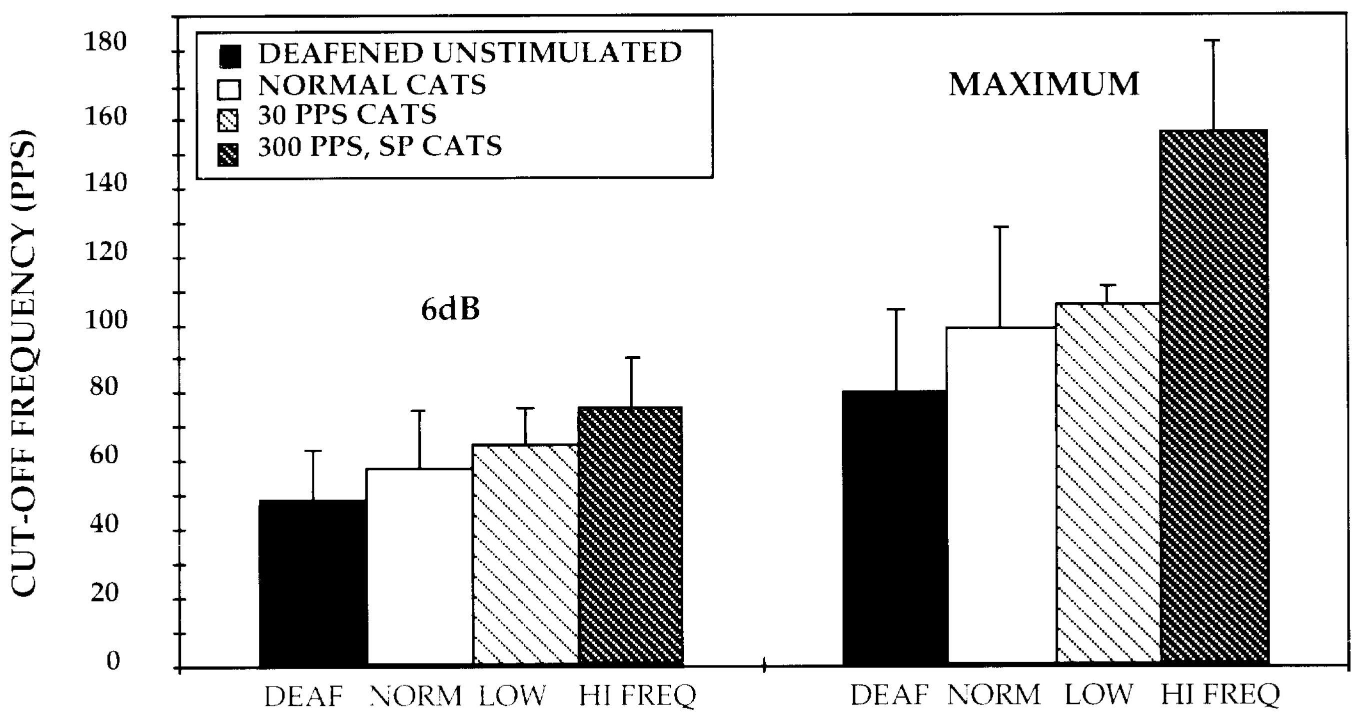

Figure 2. Chronically stimulated animals were presented with varied stimuli as shown in Table 2. Comparing the maximum following capacity of these animals sorted by chronic stimulus frequency clearly demonstrates that the frequency of stimulation strongly effects the changes in temporal resolution seen in neurons in the IC.

The results of statistical analyses of the maximum cut-off frequencies for each group are tabulated in Table 4. Although recently deafened animals were able to follow pulse trains at higher rates than long deafened, unstimulated cats this difference was not statistically significant (p-value = 0.14). In contrast, both groups of unstimulated animals were significantly different than the chronically stimulated animals as a whole (the "All Stimulated" category, p-value = 0.001-0.003). Sorting the stimulated animals according to the frequency of the chronic stimuli they received (see Table 3) and comparing these subgroups to the unstimulated animals clearly demonstrates that the temporal characteristics of the chronic stimulus are the primary factor determining changes in the capacity of these neurons to resolve rapidly delivered pulsatile signals. The difference between the average cut-off frequency for the fast stimulation group and all other groups is highly significant (p-value = <0.0001 - 0.0003).

	Normal	Unstim.	All Stim.	Stim. Slow	Stim. Fast
Normal					
Unstimulated	0.14				
All Stimulated	0.001	0.003			
Stimulated Slow	0.28	0.02			
Stimulated Fast	<0.0001	0.0002		0.0005	

TABLE 4. P Values for the statistical comparison of temporal responses (maximum cut-off frequency) for animal groups with different deafening and stimulation histories.

It is important to note that these stimulation based differences were observed after chronic stimulation with either pulsatile or analog higher frequency stimuli. These signals were generated by a DSP-based signal generator (300 Hz carrier modulated at 30 Hz) in three of the animals and by a single channel analog speech processor (filtered to deliver a bandwidth of 200-700 Hz) in the other four animals. Both of these systems, which we defined as "high" frequency in this study, are actually relatively low in frequency compared to the rates applied in clinical devices. Currently used signal processors based on the CIS strategy use pulse trains of up to 1,500 pps with modulation rates which begin significantly above 30 Hz and exceed 2 Khz. Typical analog speech processors are open ended but assign the most basal electrodes in the cochlea a frequency range above 2 KHz. If we further divide the our "fast" group of animals into those which received 300Hz/30Hz stimulation and those which received speech processor stimulation their average maximum cut-off frequencies are 147.7 pps and 156.5 pps, respectively. Because there is no control or measurement of the spectral structure of the speech processor signal in these animals it is impossible to define the stimulation they have actually received. Although there is some indication that the animals receiving potentially higher rate stimuli from the speech processor may have faster temporal resolution than animals receiving a 300Hz/30Hz modulated signal, it should be noted that this difference is not statistically significant (p-value = 0.32, not shown).

These data clearly substantiate the conclusion that chronic electrical stimulation of the auditory system induces changes in the temporal response properties of neurons in the IC. Moreover, the exact stimuli used in chronic stimulation, particularly the frequency characteristics, significantly affect the extent of these changes. The frequency-dependent effects of chronic stimulation in altering the capacity of midbrain neurons to resolve relatively fast temporal events may be important in understanding differences between the performance of some cochlear implant users and in understanding how these patients improve over time. Future experiments in which acutely deafened adult cats and long deafened animals will be implanted and chronically stimulated will be of particular interest in addressing these questions.

Evoked Potential Monitoring as a Measure of Temporal Resolution

During the past quarter we have initiated the study of two methods to passively evaluate the temporal resolution of auditory neurons to electrical stimulation. The first of these methods uses scalp recorded auditory brainstem responses to stimuli delivered at varied intervals. The second technique was developed by Drs. Charles Finley and Blake Wilson to measure the temporal capacity of the auditory periphery directly in cochlear implant patients. This method employs inactivate contact sites on a multichannel intracochlear electrode as recording electrodes to measure the intracochlear compound action potential (CAP) generated in response to electrical stimuli delivered at other contact sites. Both of these techniques may provide a valuable reference between current animal and human studies which each offer valuable, but previously incomparable, sets of performance data.

Figure 3 illustrates preliminary data from EABR measurements in three animals. By recording the electrically evoked response to pulse trains delivered at different presentation rates, in this case 50 pps to 8 or 9 pps, this technique provides a simple measure of temporal resolution which can be tested throughout the chronic stimulation period of any animal. Using this measure repeatedly will allow us to track changes in temporal capacity which occur during, or following, different stimulation and behavioral training regimens and compare these results directly with data recorded from the inferior colliculus in the final electrophysiology experiment. In the future these data from different deaf animal models with various degrees of cochlear pathology may also be compared with similar recordings in human subjects with known cochlear implant performance.

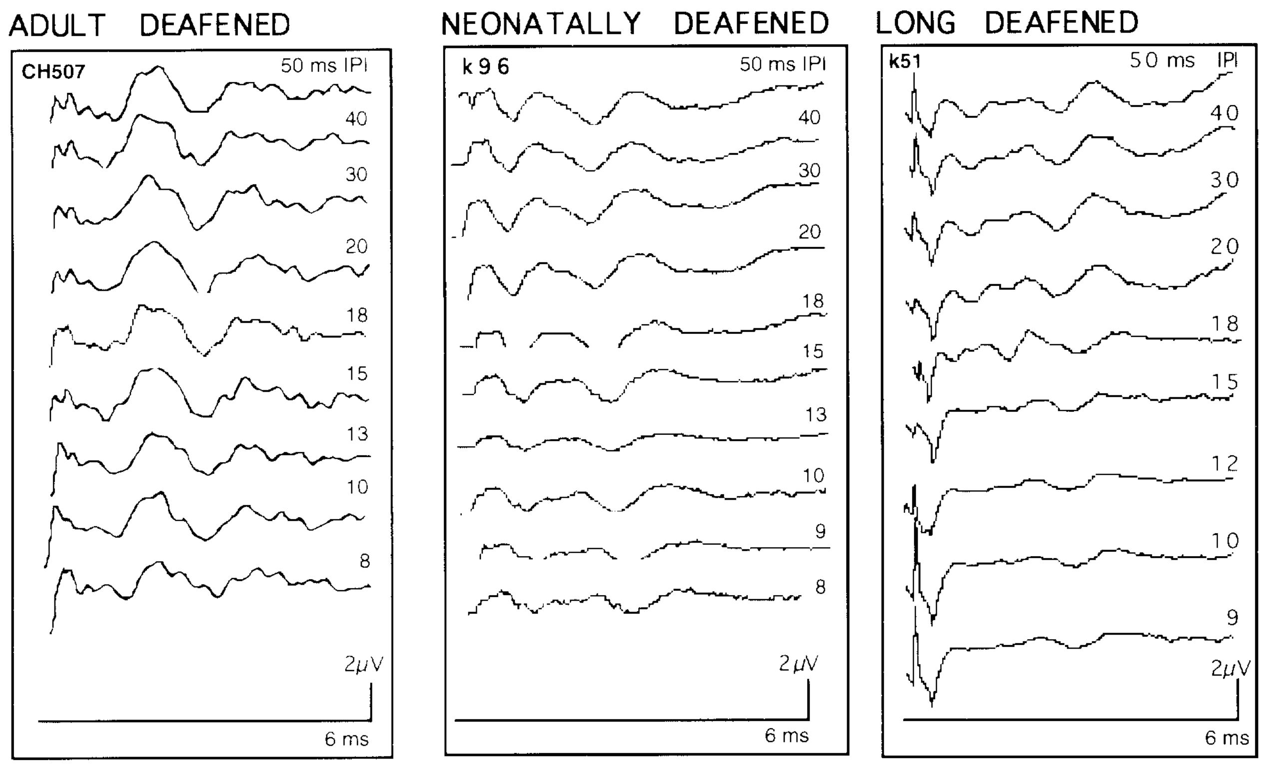

Figure 3. Auditory brainstem responses to electrical pulses delivered at decreasing interpulse intervals are shown above for three cats. The two animals on the left have been implanted and chronically stimulated. The third cat (K51) was neonatally deafened, implanted at age four years and immediately tested. Adaptation of the EABR response at higher stimulus presentation rates is most visible in the long deafened, unstimulated animal.

Intracochlear Evoked Potentials, 33 µsec/phase pulses

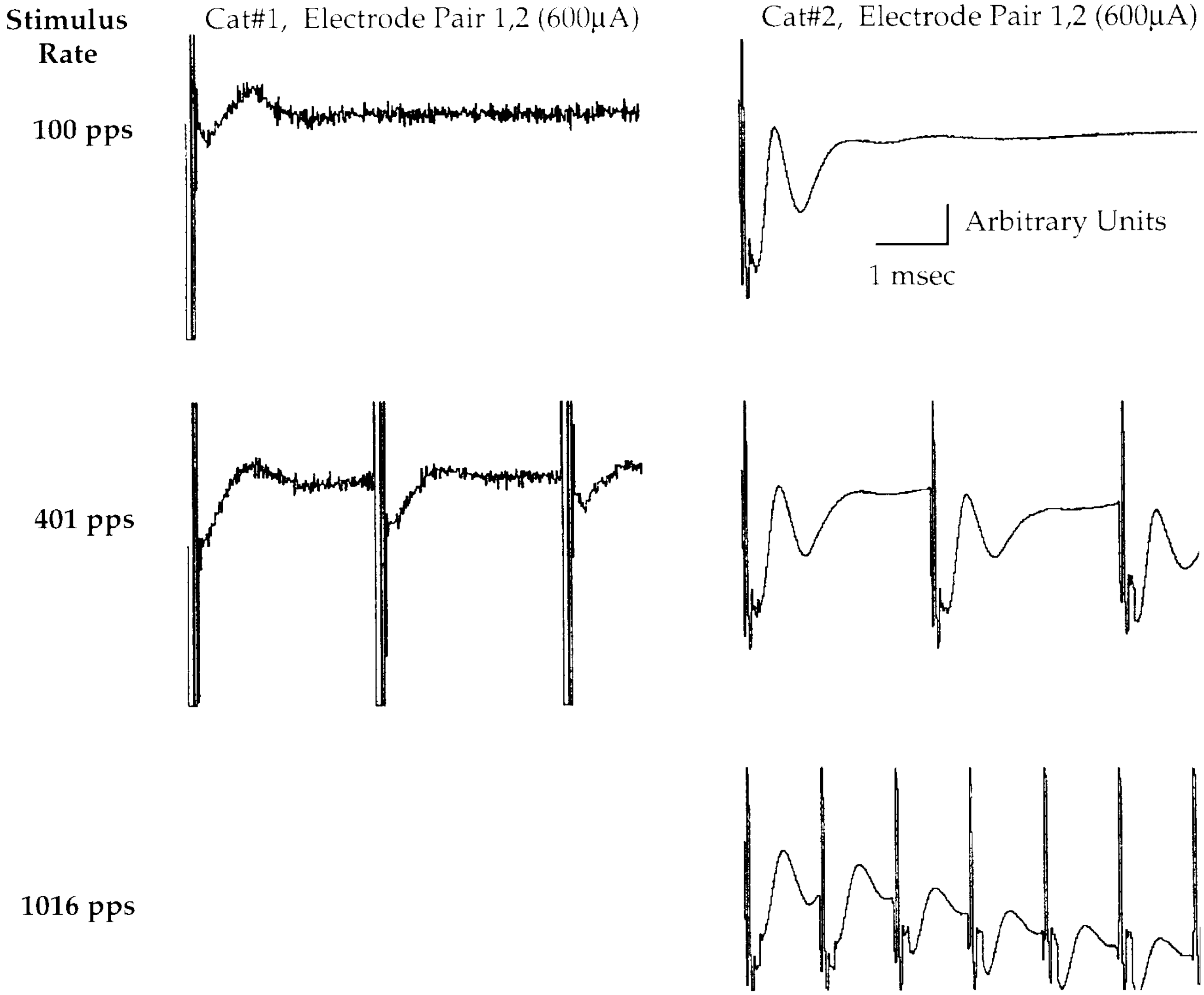

Figure 4. Compound action potential recordings in two cats using 33 µsec/phase biphasic pulse trains of varying pulse rate (100, 401 and 1016 pulses per second). Cat #1 (K51) was a long term neonatally deafened animal implanted at age five years. These recordings were made prior to chronic stimulation. Cat #2 was neonatally deafened, implanted and stimulated for eight months prior to these measurements. Note the differences in CAP shape, amplitude and duration which immediately follows each electrical signal artifact for the two cats.

During the past quarter we successfully recorded intracochlear compound action potentials to electrical stimulation with in collaboration with Dr. Charley Finley, who traveled from Research Triangle Institute to consult on this research. In this collaboration we hope to duplicate the equipment, techniques and parameters used at RTI to measure CAPs in human cochlear implant subjects. The recordings shown in Figure 4 were made using an unactivated, basal electrode contact as the active recording lead while bipolar stimulation was delivered *via* apical electrode contacts #1 and #2. Additional subcutaneous silver wire recording electrodes were used on the vertex of the skull (reference electrode) and in the skin below the contralateral pinna (recording ground lead). Responses to 500 stimuli were averaged and recorded for each pulse rate tested.

The responses of these two animals differ in several ways. First, the response of the second animal contains a clear negative wave following the initial positive deflection. The recording from the long deafened, unstimulated animal (#1) does not show this negative waveform. Second, the CAP response of the chronically stimulated animal does not adapt noticeably at higher stimulus presentation rates while the response of the first cat to the second pulse at 401 pps is almost eliminated. It should be noted that these animals are two of the same cats (K51 and K96) for which EABR data were shown above. The parallel findings between these two independent measures are very encouraging. Continued evaluations are planned, deriving CAP responses, ABR data as presented above and unit data from the inferior colliculus in these cats and four other animals now undergoing chronic stimulation. In the future we believe that these parallel measurements will reveal additional insights into the mechanisms underlying changes in the central auditory system consequent from deafening and chronic electrical stimulation with a cochlear implant. Future comparisons with equivalent measures in human subjects participating in clinical research at RTI also hold great promise.

Work for the Next Quarter

1. Data analysis for three acute electrophysiology experiments conducted during the last quarter will be completed. This results will include additional data for inferior colliculus units responding to pulse trains of varied carrier and modulation frequencies as well as modulation transfer functions to assess temporal resolution and "mapping" of the spatial spread of excitation for stimulated and unstimulated electrode combinations.

2. We will continue the behavioral training of two neonatally deafened, litter matched kittens. These two animals are being stimulated with identical signals in a "yoked" paradigm, in an effort to separate the effects of cognitive attention from those of passive stimulation. In this protocol, one cat is being actively trained animal and tested in the discrimination of different modulation rates of a 300 Hz carrier. The second animal receives the identical signal passively, i.e., without behavioral significance. Both of these animals will complete this series of behavioral training/passive stimulation and will be scheduled for acute electrophysiology experiments during the next quarter.

3. An acutely deafened adult cat has now been chronically stimulated for a period of eight weeks. This stimulation will be continued into the next quarter and an acute electrophysiology experiment is planned for this animal at the end of that period.

4. We will initiate behavioral training of one long-term neonatally deafened cat that was implanted during this past quarter.

5. We will continue to measure temporal response characteristics of all implanted cats as an adjunct to regularly scheduled ABR threshold measurements. Both ABRs and intracochlear CAP recordings to varied rate stimuli will be collected as time and equipment permit.