6th Quarterly Progress Report
January 1, 1996 to March30, 1996

Fundamental Neurosciences Contract N01-DC-4-2143

Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

Submitted by:

Ralph E. Beitel, Ph.D.
Stephen J. Rebscher, M.S.
Patricia A. Leake, Ph.D.
Maike Vollmer, Ph.D.

Epstein Hearing Research Laboratories
Department of Otolaryngology, Room U490
University of California, San Francisco
San Francisco, Ca 94143-0526

ABSTRACT

In this Quarterly Progress Report we present progress in psychophysical studies conducted in neonatally deafened, chronically implanted cats. Earlier behavioral results showed that the detection thresholds and reaction times (behavioral latencies) both decreased in deaf cats when the duration of a 100 Hz electrical sinusoidal stimulus was increased from 0.03-sec to 0.1-sec duration. In addition, detection thresholds for an even longer duration (1 sec) electrical sinusoid were significantly lower (as much as 15 dB in some animals) than minimum electrophysiological thresholds for neurons in the inferior colliculus (IC) and the primary auditory cortex (AI). These results indicated that stimulus duration can have a very significant effect on detection threshold for 100 Hz sinusoidal stimuli and suggested the hypothesis that behaviorally significant temporal integration may occur within 100 msec after stimulus onset. In the present report, investigation of temporal integration has been extended in two additional behavioral detection experiments designed specifically to examine this hypothesis.

In addition, in this Progress Report we also present a description of a new behavioral paradigm and initial results obtained with signals that more closely approximate those used in signal processing strategies for cochlear implants. In this new paradigm the cats are required to actually *discriminate* a change in the rate or cadence of the AM pulse train to avoid a mild electrocutaneous shock. This task requires successive comparison of AM stimuli, and thus is qualitatively different from all previously reported psychophysical experiments which required only the simple detection of a stimulus. Thus, the preliminary psychophysical results presented in this report represent the first example of successive discrimination of electrical stimuli in our deaf animal model.

Psychophysical Studies of Temporal Processing of Electrical Pulses Delivered by a Cochlear Implant in Neonatally Deafened Cats

Temporal processing in the auditory system may be divided into two general categories: temporal integration and temporal resolution. Temporal integration or temporal summation refers to a reduction in psychophysical detection threshold when the duration of a signal is increased; temporal resolution refers to an observer's ability to detect two or more events as temporally distinct. Both of these processes are important in listening for normal hearing, impaired hearing, and deaf (electrical hearing) human subjects (Carlyon, et al, JASA, 1990, 87, 260-268; Donaldson, et al. ARO Abstr., 1995, 18, 179; Viemeister & Wakefield, JASA, 1991, 90, 858-865).

In a previous report (QPR #1, Sept. 30-Dec. 31,1994; current Contract), results were presented showing that detection thresholds and reaction times (behavioral latencies) both decreased in deaf cats when the duration of a 100 Hz electrical sinusoidal stimulus was increased from 0.03-sec to 0.1-sec duration. In addition, data were presented showing that for an even longer stimulus duration of 1 sec, psychophysical thresholds were significantly lower than minimum electrophysiological thresholds for neurons in the inferior colliculus (IC) and the primary auditory cortex (A1). Taken together, these results indicated that stimulus duration has a significant effect on detection threshold for 100 Hz sinusoidal stimuli and suggested the hypothesis that behaviorally significant temporal integration occurs within 100 msec of stimulus onset in the feline deafened auditory system. In the present report, investigation of temporal integration has been extended in two simple behavioral detection paradigms designed specifically to examine this hypothesis in a manner that will allow precise comparisons of behavioral threshold data with single unit and multiunit electrophysiological results obtained from the IC and the A1 with the same range of stimulus durations.

In this report we also describe a new experimental paradigm designed to investigate temporal resolution in the auditory system of the deafened cat, with signal characteristics (pulse width, pulse frequencies, modulation rates) that more closely approximate those used in signal processing strategies for cochlear implants. In this new behavioral paradigm, amplitude modulated (AM) bursts of biphasic electrical pulses were delivered to the cochlea, and the cat was required to discriminate a change in the rate or cadence of the AM pulse train to avoid a mild electrocutaneous shock. Thresholds for different carrier frequencies were estimated by determining the AM rate that was discriminated from the standard AM rate on 50% of "warning" trials. Because this task (in contrast to simple detection of a stimulus) requires successive comparison of AM stimuli, the AM paradigm is qualitatively different from all previously reported psychophysical experiments in deaf animal models for electrical hearing. Preliminary psychophysical results presented in this report represent the first example of successive discrimination of electrical stimuli in a deaf animal model.

METHODS

A detailed description of the deafening and psychophysical procedures has been reported previously (QPR #5, July 1-Sept 30, 1992, Contract #N01-DC-1-2400). Figure 1 summarizes the individual histories of a group of 4 animals for which data are presented in this report. Briefly, cats were deafened neonatally by injection of ototoxic drugs and chronically implanted at 6 to 8 weeks of age with feline intracochlear electrodes consisting of four to eight electrode contacts driven as bipolar pairs. The profoundly deaf kittens were chronically stimulated either with a single channel speech processor or with computer generated electrical pulse trains (300 pps, amplitude modulated at 30 Hz) for an initial period of several weeks until they are judged to be mature enough to undergo behavioral training. The cats were then trained in a conditioned avoidance paradigm to lick a metal spoon on "safe" trials to obtain a preferred food reward (meat puree) and to interrupt licking on "warning" trials to avoid a mild electrocutaneous shock. During training, suprathreshold electrical stimuli were delivered to the cochlea as warning signals on 20 to 30% of trials. Once performance was stable, threshold estimates (50% avoidance) were obtained using the psychophysical method of constant stimuli. Stimulus generation and data acquisition were under computer control during experimental sessions (see Figure 2 on the following page).

Cat #	Date of Birth 1993	Age at Stim. Weeks	Passive Stim. Current µAmps	Passive Stim Freq.	Passive Stim. Period Weeks	Behav Train Period Days	Behavioral Training Task	Age At Sac. Weeks
K 96	24-Jan	7	25-50	Sp. Proc.	29	87 23	Thresh. Mod. Discrim.	44*
K 98	12-Mar	7	25-50	Sp. Proc.	22	121 23	Thresh. Mod. Discrim.	39
K 99	22-May	8	32-100	300/30	12	141	Mod. Discrim.	49
K 00	22-May	8	125	300/30	12	141	Mod. Discrim.	45

Figure 1. Individual histories of the 4 animals studied in these psychophysical experiments. Animal #K96 was yoked to K98 during the final 7 weeks of the training period and K00 was yoked to K99 for the final 15 weeks of training. (*Device failed during chronic stimulation and animal was reimplantated)

Figure 2. (Following page) Training session panel from the computer controlled psychophysics laboratory. During training and testing sessions, the "virtual" panel is displayed on a monitor. Stimulus parameters can be changed directly by selecting them with the mouse. Response parameters (# of trials, # of shocks, etc.) are updated following each trial. At the conclusion of a session

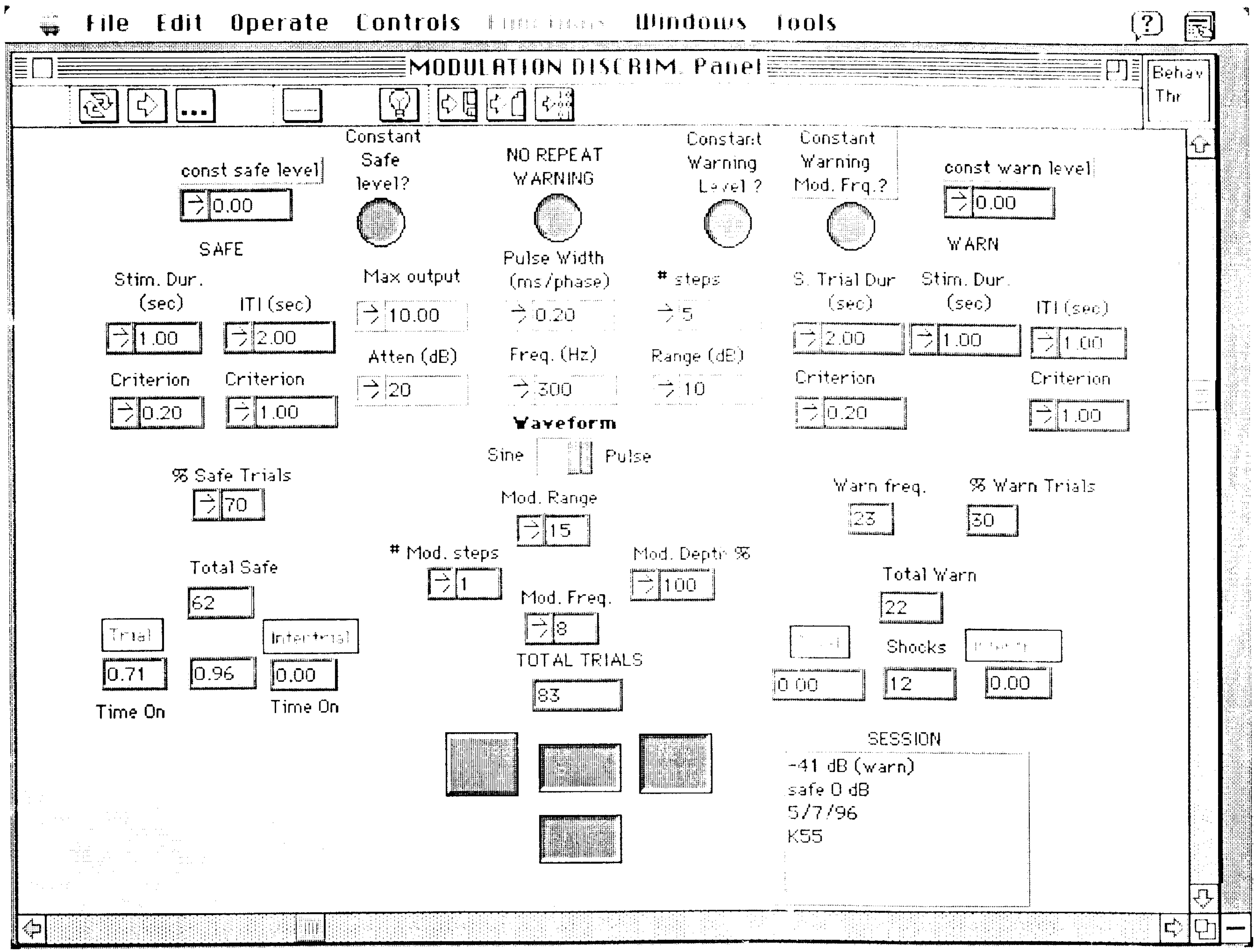
File Edit Operate Controls Windows Tools
MODULATION DISCRIM. Panel
Behav
Thr
const safe level
0.00
SAFE
Constant Safe level?
NO REPEAT WARNING
Constant Warning Level ?
Constant Warning Mod. Frq.?
const warn level
0.00
WARN
Stim. Dur. (sec)
1.00
ITI (sec)
2.00
Criterion
0.20
Criterion
1.00
Max output
10.00
Atten (dB)
20
Pulse Width (ms/phase)
0.20
Freq. (Hz)
300
steps
5
Range (dB)
10
S. Trial Dur (sec)
2.00
Stim. Dur. (sec)
1.00
ITI (sec)
1.00
Criterion
0.20
Criterion
1.00
Waveform
Sine
Pulse
% Safe Trials
70
Mod. Range
15
Mod. steps
1
Mod. Depth %
100
Mod. Freq.
8
Warn freq.
23
% Warn Trials
30
Total Safe
62
Trial
0.71
Time On
0.96
Intertrial
0.00
Time On
TOTAL TRIALS
83
Total Warn
22
Shocks
0.00
12
0.00
SESSION
-41 dB (warn)
safe 0 dB
5/7/96
K55

Figure 2

1. TEMPORAL INTEGRATION EXPERIMENTS

In these studies, 5.0 msec/phase biphasic square-wave pulses were used during threshold testing sessions in which a cat was required to detect the stimulus to avoid a mild shock. Two experimental variations were used to evaluate temporal integration. In the first variation, two pulses were presented on each "warning" trial and the interpulse interval (IPI) was varied across sessions (2.5, 10.0, or 490.0 msec). Figure 3 depicts the detection thresholds obtained in two cats, K96 and K98, for the 3 IPI values tested. The curves are essentially flat, indicating that when two biphasic pulses (5.0 msec/phase) were presented at short IPIs (2.5 and 10.0 msec), thresholds were the same as thresholds for widely separated pulses. This result indicated that temporal integration did not occur under the conditions of this experimental variation.

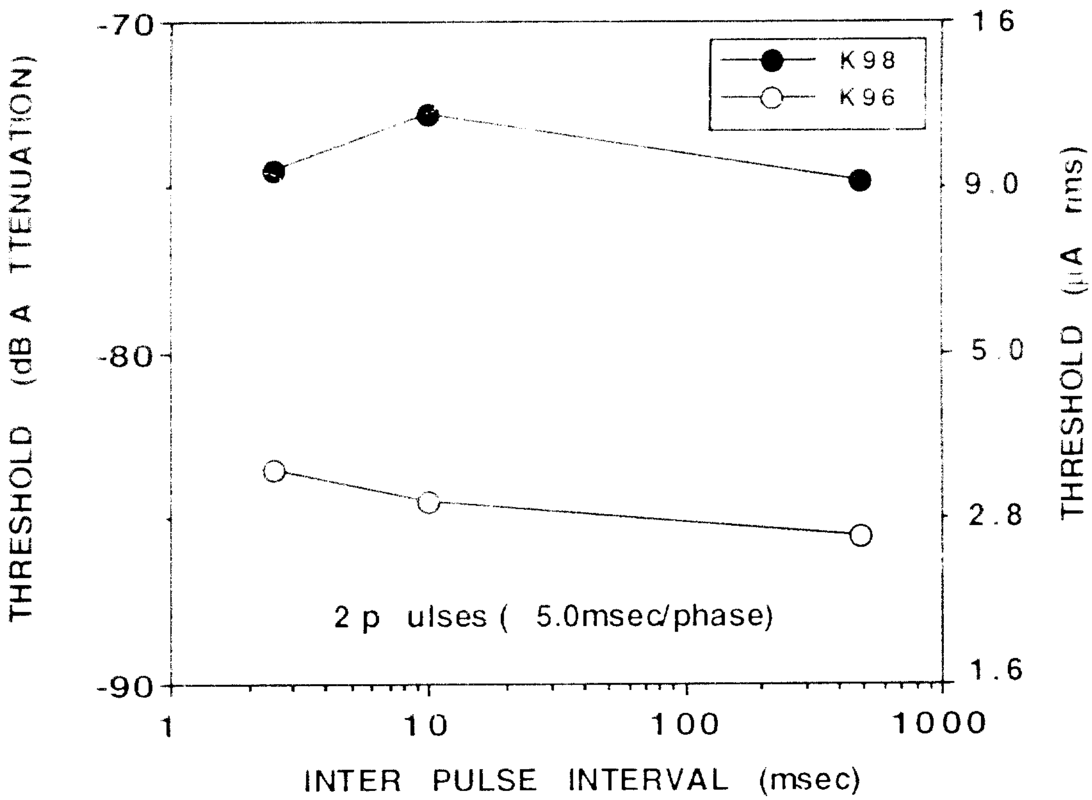

Figure 3. Psychophysical thresholds (in dB attenuation and µA) for detecting 2 pulses are shown as a function of interpulse interval (in msec). Each curve represents the thresholds for one cat. Stimuli were biphasic pulses with a phase duration of 5.0 msec.

In the second variation of this behavioral paradigm, a train of pulses was presented on each "warning" trial, and with the IPI held constant at 2.5 msec, the number of pulses was varied across testing sessions to produce stimulus trains of increasing duration. The stimuli consisted of 1, 2, 8, 24, or 80 pulses and the corresponding stimulus durations for these pulse trains were 0.01, 0.025, 0.1, 0.3, and 1.0 sec, respectively. Figure 4 shows the detection threshold results obtained in these same two cats (K96 and K98) for the 5 electrical stimuli. For both cats, detection thresholds clearly decreased with increasing train durations. In K96 the threshold was 7.9 dB lower for a 1.0-sec duration train as compared to the shortest train duration (25.0 msec duration), and in K98 the threshold was 8.6 dB lower for the 1.0-sec duration stimulus. These data suggest that significant temporal integration occurs under the conditions of this experimental variation. This result highlights the importance of including stimulus duration (or number of pulses) as a parameter whenever psychophysical and electrophysiological thresholds are compared for electrical stimulation of the cochlea. The psychophysical results and comparison electrophysiological results will be discussed in the context of models of the integration process in a later progress report.

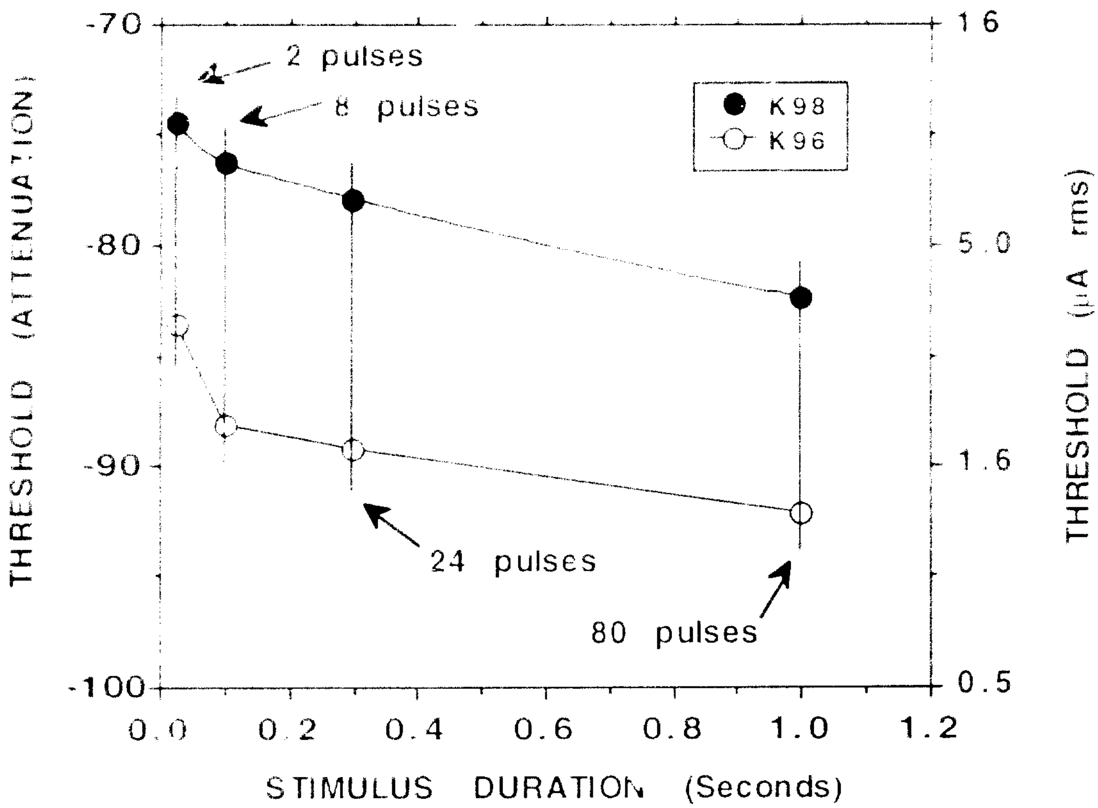

Figure 4. Psychophysical detection thresholds (in both dB attenuation and µA) as functions of stimulus duration in seconds for trains of biphasic pulses. Each curve represents the thresholds for one cat. The numbers on the graph indicate the number of pulses (5.0 msec/phase) comprising the train for that particular stimulus duration.

2. TEMPORAL RESOLUTION. AMPLITUDE MODULATION EXPERIMENTS

In this paradigm, an AM train of 0.2 msec/phase biphasic pulses was presented for a duration of 1 sec at carrier frequencies of either 100, 300, or 500 pps during different testing sessions (Fig. 5). Envelope peak amplitudes were set at 3 dB above amplitude detection thresholds; modulation depth was 100%. On "safe" trials, the AM rate was 8 Hz (standard rate). On each "warning" trial one of five higher AM rates (comparison rates) was presented. The cat was required to discriminate the change in cadence between signals presented on "safe" and "warning" trials (successive discrimination) to avoid a mild shock.

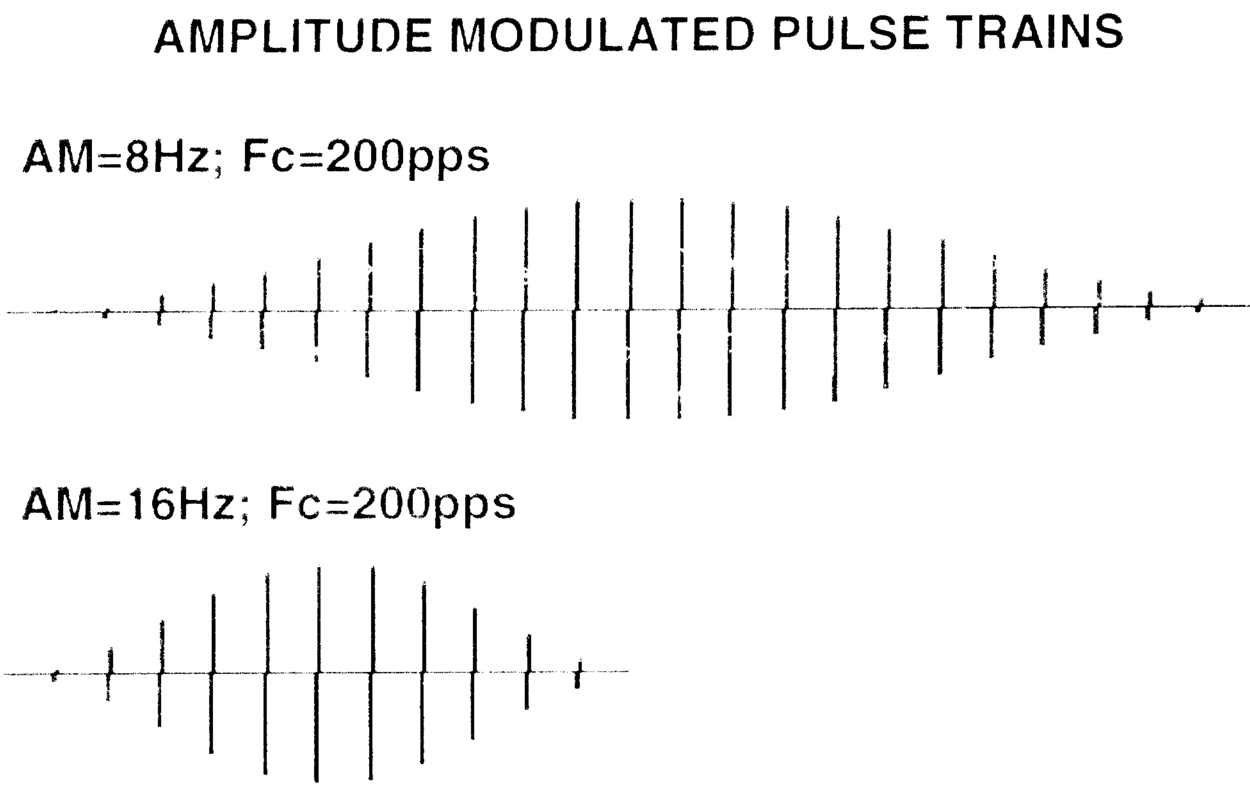

Figure 5. Amplitude modulated signals. The carriers used in psychophysical experiments are 0.2 msec/phase biphasic pulses presented at rates of 100, 300, or 500 pps. Modulation depth=100%. **A.** "Safe" (standard signal) AM=8Hz; carrier=200 pps. **B.** "Warning" (comparison) signal AM=16 Hz; carrier=200 pps.

As previous work from this laboratory has shown, chronic electrical stimulation of the cochlea in the deaf cat may profoundly alter temporal processing in the central auditory system, presumably representing one form of induced "plasticity". One objective of current studies is to investigate the potential consequences of actively attending to conditioned AM signals (as opposed to effects of passive or unconditioned stimulation) on temporal processing in the central auditory system. In this experiment an unconditioned control cat (K96 and K100) was "yoked" to each of the two experimental cats (K98 and K99). During behavioral training and testing sessions, the "yoked" control was placed in a cage adjacent to the testing chamber and received AM stimuli on "safe" and "warning" trials with envelope and carrier frequencies identical to those applied to the experimental (conditioned) animal. However for the "yoked" controls, the AM stimuli were not associated with food or shock. That is, the stimuli had no behavioral consequences and could be ignored. In subsequent physiological experiments, identical stimuli were used to investigate temporal processing within the inferior colliculus and in primary auditory cortex in the control and experimental animals. The electrophysiological results will be reported in a later progress report.

Preliminary results from psychophysical studies using this amplitude modulation discrimination task are shown in Figs. 6 and 7, which present psychometric functions for one cat (K99). Figure 6 shows data for discrimination of electrical signals with carrier rates of 100, 300 and 500 pps. The psychometric functions show the cat's performance in discriminating the standard modulation frequency (8 Hz AM) from various comparison modulation frequencies. The psychophysical thresholds are defined as the ΔHz required for the cat to discriminate at 50% avoidance. The data show that for the three carrier rates of 100, 300 and 500 pps, the cat performed at the criterion level when the comparison modulation frequencies were 16 Hz, 17.8 Hz and 19.6 Hz, respectively (Fig. 6). Thus, the psychophysical thresholds (ΔHz from 8 Hz) for these signals were 8.0, 9.8, and 11.6 Hz, respectively. It is unclear from these preliminary data whether the orderly increase in ΔHz with increasing carrier frequency represents a real trend in the data or whether it merely reflects variability in performance. The latter interpretation is suggested by the psychometric functions shown in Fig. 7. These are data taken from sessions that were run during three different periods of testing with a carrier of 300 pps. The range of ΔHz required for the cat to perform the identical psychophysical task at the 3 different times is 8.0 to 10.8 Hz, essentially the same as that observed with different carrier frequencies. Thus there appears to be significant variability in performance of this discrimination task that may account for the range of thresholds shown in Fig. 6.

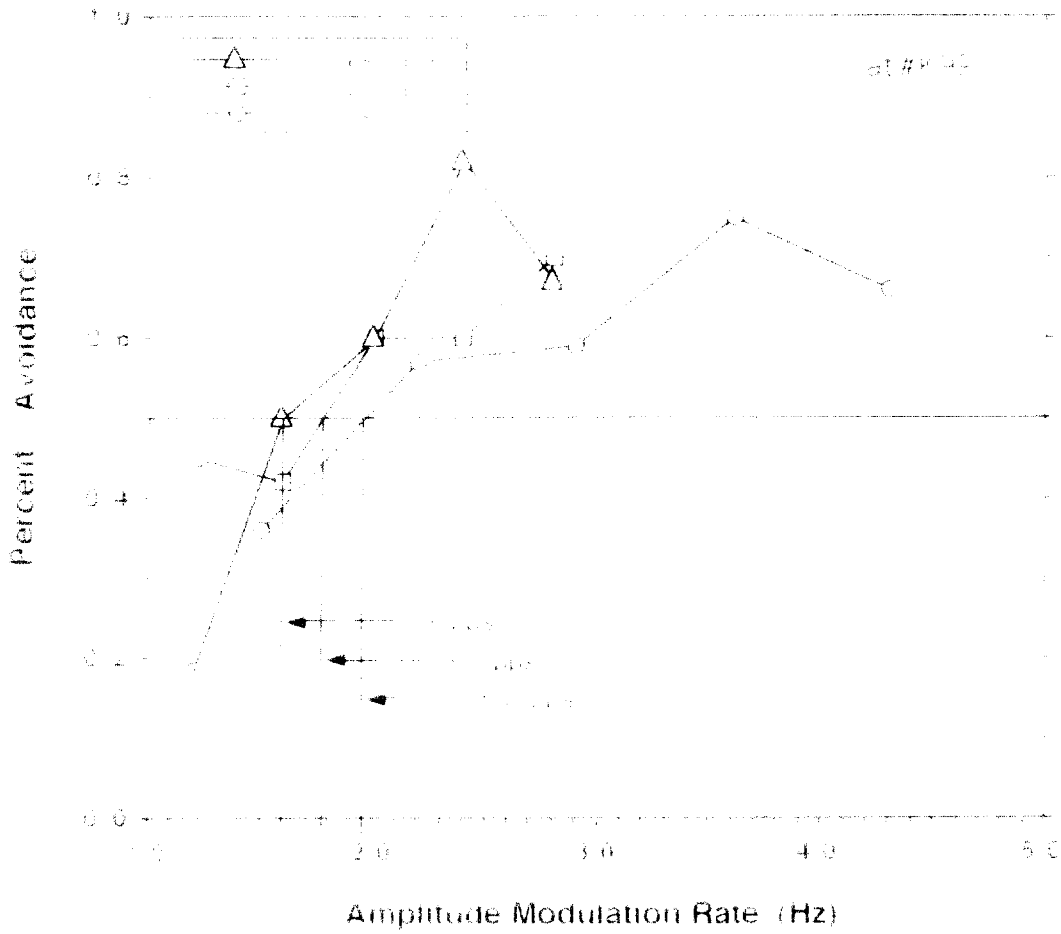

Figure 6 [illegible] functions for cat K[illegible] at carrier frequencies of [illegible] and [illegible] pps [illegible] as estimated by interpolation, are indicated by arrows [illegible] abscissa. In the text, thresholds are expressed as frequency difference [illegible] AM[illegible] AMF). K[illegible] was trained and tested extensively with a carrier of [illegible] before and after brief periods of testing with carriers of [illegible] and 500 pps.

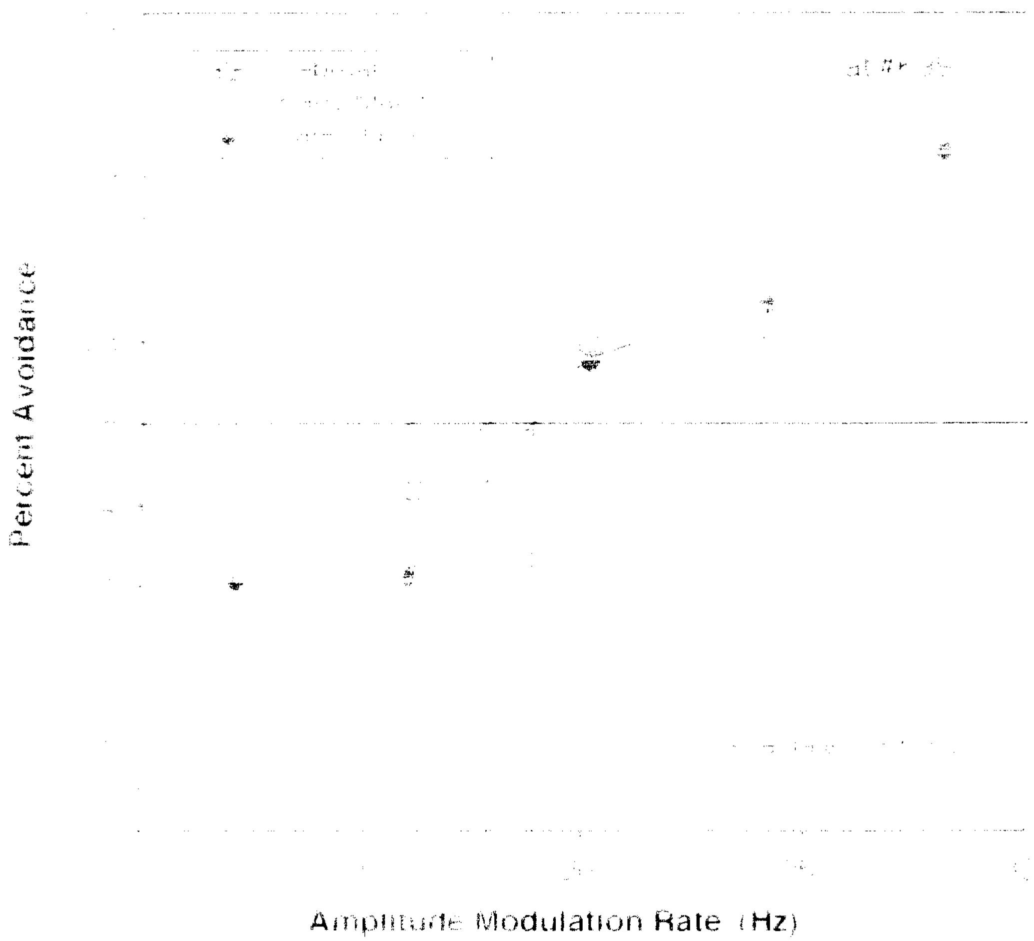

Figure 7. [illegible] functions for cat K[illegible] at three different testing periods [illegible] [illegible] Thresholds ([illegible] avoidance) estimated [illegible] indicated by arrows on the abscissa.

Although these preliminary results indicate that both thresholds and [illegible] high for a standard 8 Hz AM stimulus, the success in [illegible] a successive temporal discrimination task is very encouraging. [illegible] paradigm (successive discrimination) can be used in future studies to investigate temporal resolution in the deafened auditory system and also can be adapted to [illegible] a successive spatial discrimination task [illegible] successive [illegible] different pairs of electrode contacts.

SUMMARY

1) Psychophysical data have been obtained on processing of temporal information (temporal integration, temporal resolution) in the deaf feline model developed at UCSF. The psychophysical experiments were designed so that specific quantitative comparisons may be made with data from physiological experiments (microelectrode recordings at IC and AI). Comparisons between psychophysical and electrophysiological results will be presented in a later progress report.

2) Two deaf cats have been trained on an amplitude modulation task that required successive discrimination between a standard stimulus and comparison stimuli.

3) The data presented above are potentially important as model results for understanding temporal processing and changes in temporal processing that develop with use of cochlear implants in deaf humans.

Work Planned for the Next Quarter

1. Data analysis for electrophysiology experiments conducted during the last quarter will be continued. 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 combination. Data to be analyzed include two pairs of animals that were stimulated in the "voked" paradigm as described in this QPR. Correlations of behavioral and electrophysiological data and analyses of histological data are also in progress.

2. An acutely deafened adult cat that had been chronically stimulated for a period of almost 3 months damaged it's implant this past quarter; reimplantation was unsuccessful and the animal was euthanized for histological studies. A second adult cat is presently undergoing stimulation which will be continued into the next quarter. A second adult deafened cat will be implanted during the next quarter.

3. Behavioral training of one long-term neonatally deafened cat will continue. Detection thresholds have been defined and we are currently attempting to train this cat on the AM discrimination task.

4. Measurements of temporal response characteristics in all implanted cats will be continued as an adjunct to regularly scheduled ABR threshold measurements. Both ABRs and intracochlear CAP recordings to varied rate stimuli are being collected as time and equipment permit.