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Protective Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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

ABSTRACT

This report presents results suggesting that the electrically evoked auditory brainstem response (EABR) provides a non-invasive method of assessing temporal resolution of the central auditory system in deafened cats. EABR responses to 200 µsec phase biphasic pulses of alternating polarity were recorded, and the amplitude of wave III was measured systematically for stimulation frequencies of 20 to 250 pps. Data were obtained from three groups of deafened cats representing different models of deafness (prior normal adult deafened, neonatally deafened and long term neonatally deafened). Baseline measurements (unstimulated condition) were recorded immediately following cochlear implantation and compared to measurements made after intervals of chronic intracochlear electrical stimulation. These longitudinal measurements are used to evaluate the effects of chronic stimulation on temporal resolution.

The results indicate that in all animals and under all conditions (unstimulated and longitudinal measurements during chronic stimulation) the amplitudes of EABRs decrease as stimulus frequency increases. Unstimulated adult and neonatally deafened animals displayed initial responses that were similar in amplitude. In contrast, long deafened animals demonstrated significantly reduced EABR response amplitudes. However, when temporal resolution was examined by plotting frequency transfer functions (*relative* response amplitudes for increasing stimulus frequencies) no difference was observed among the three groups of unstimulated animals. Following chronic stimulation a significant increase in temporal resolution was seen in the neonatally deafened cats, as indicated by increased relative amplitudes of EABR responses for stimulus frequencies over a range of about 90-150 pps. In contrast, preliminary data in 2 adult deafened animals indicate that the temporal resolution is unchanged following several months of chronic stimulation. Preliminary data in 2 chronically stimulated long deafened animals show opposite trends and thus are considered too limited to draw even preliminary conclusions. These findings indicate that the EABR may provide useful information on the temporal resolution of the central auditory nervous system. Further, they suggest that this capacity of the central auditory system may vary depending upon previous auditory experience, duration and timing of deafness and duration of experience with electrical stimulation.

ELECTRICALLY EVOKED AUDITORY BRAINSTEM RESPONSES AS A MEASURE OF TEMPORAL RESOLUTION

EABR data from 16 cats are included in this report (5 prior normal adult deafened, 8 neonatally deafened and 3 long deafened animals). Table 1 presents the stimulation histories for all animals. Animals were evaluated by EABR measures immediately following cochlear implantation. These initial measurements represent the unstimulated condition. Additional measurements were made during and after 4-6 months of chronic electrical stimulation.

Methods

The methods for deafening, cochlear implantation, electrophysiology and chronic stimulation have been described in previous reports. Brief descriptions of the procedures are reviewed below.

Deafening

For neonatal deafening animals received daily IM injections of neomycin sulphate (50-60 mg/kg/day) beginning 24 hours after birth. Injections were given for 16-21 days. Auditory brainstem responses (ABRs) to clicks (200μs/phase, 20/sec) and frequency following responses (FFRs) to 500 Hz tones (5/sec) were obtained for each ear at day 16. Profound hearing loss was confirmed by absence of response to either stimulus at equipment limits (100 dB peSPL). If responses were present neomycin injections were continued and hearing reassessed at 21 days. All animals included in this study had no evidence of residual hearing.

Adult animals were deafened by coadministration of ethacrynic acid and kanamycin as described by Xu et al. (1993, Hearing Res. 71:201-215). Animals were sedated with an IM injection of ketamine and acepromazine and an intravenous catheter inserted. A baseline ABR intensity series was collected and threshold determined visually. Kanamycin (300 mg/kg) was injected subcutaneously and ethacrynic acid (1mg/min) intravenously infused until no response was obtained to click evoked ABRs at equipment limits. ABRs were monitored for 4 hours following deafening.

CHRONIC STIMULATION HISTORIES

	ID#	CURRENT (μA)	FREQUENCY (pps)	LENGTH (wks)
	90-158	100-200	300/30	20
Adult	401.3	100-126	300/30	19
Deafened	HD-159	79-200	NA	
	93-087	90-120	300/30	28
	95-487	75-120	300/30	24
Neonatally	K101	79-200	300/30	37
Deafened	K102	79-158	300/30	30
(<1 yr. old)	K104	36-141	300/30	26
	K105	63-126	800/60	13
	K96	25-160	SP, Beh*	37
	K98	25-100	SP, Beh*	32
	K106	25-100	800/50	23
	K107	25-100	800/17	14
Neonatally	K55	36-112	Beh*	
(Long)	K56	316-562	300/30	5.5
Deafened	CH611	25-100	300/30	3.0

**SP, speech processor; Beh, behaviorally trained*

Table 1 Electrical stimulation histories for all animals included in this study.

Cochlear Implantation

Animals were implanted at 8-10 weeks of age (neonatally deafened group) or as adults (prior normal and long deafened groups). All animals were implanted with a scala tympani electrode which consisted of four platinum-iridium wires embedded in a silastic carrier with each wire ending in a ball contact 250μm in diameter. Chronic stimulation was delivered via the more apical bipolar electrode pair for periods of 3-6 months (4 hours per day, 5 days per week).

Electrophysiology

Auditory brainstem responses to electrical stimulation were recorded differentially, amplified and bandpass filtered (DAM-50), from silver wires inserted through the skin (vertex (+), ipsilateral mastoid (-) and contralateral ground). Electrical stimuli consisted of charge balanced (capacitatively coupled) biphasic square wave pulses (200 μsec/phase) delivered to the cochlear implant via a specially designed stimulus isolation, voltage to current amplifier calibrated to deliver a 100 μAmp output for an input of 1 volt. Stimuli were generated by a TMS 3200 PC based workstation driven by custom software.

Responses were averaged for 500-1000 stimuli using a 16 bit A/D converter IBM PC. Threshold was defined as the lowest intensity level at which a repeatable response was just visible. For interpulse interval data collection EABRs were recorded at 6 dB suprathreshold for decreasing interpulse intervals of 50 ms to 4 ms, corresponding to frequencies of 20-250 pulses per second (pps). Peak to peak amplitudes were measured for wave III (2.0-2.5 ms latency), the largest and most reliable of the EABR waves.

RESULTS

Unstimulated Condition

Figure 1 (a-c) displays the individual data obtained immediately following cochlear implant surgery for the three groups of unstimulated animals. Data are plotted with amplitudes (μV) as a function of increasing stimulus frequency (pulses per second, pps) for the adult deafened, neonatally deafened and long deafened animals. Although substantial individual variability is noted, each animal demonstrates a decrease in EABR wave III amplitude with increasing stimulation frequency. The responses from the majority of adult deafened animals were less than 1 μV, although one animal (90-158) displayed highly fluctuating higher amplitude responses for some of the frequencies assessed. The majority of neonatally deafened animals have comparable amplitudes although two animals deviated from the group. Animal K107 had overall high amplitude responses and K105 had very low amplitude responses. At present data from the long deafened animals are limited, and the variability is great.

Figure 2 presents the **average** initial EABR wave III amplitudes as a function of various stimulus frequencies for the three groups of animals prior to chronic stimulation. As noted previously, EABR amplitude decreases systematically as stimulation frequency increases for each group. Despite the variability within the groups, there is

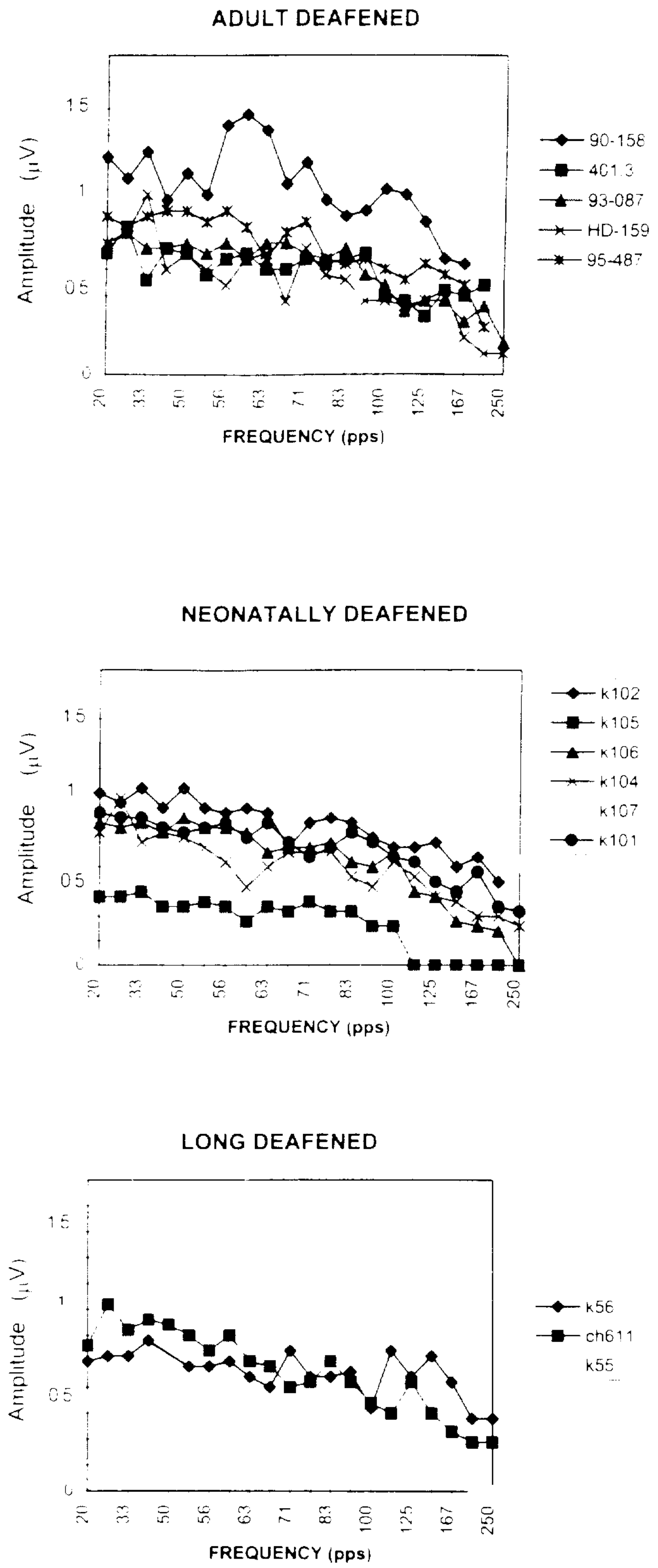

Figure 1. Absolute EABR wave III amplitudes for varying frequencies are presented. Individual data for the three groups of unstimulated animals are displayed (a-c). Data were collected for each animal immediately post implantation.

essentially no difference between the adult deafened and neonatally deafened animals in the averaged EABR amplitudes for any of the stimulus frequencies. Comparatively, the average amplitude for the long deafened animals is significantly reduced for the majority of the stimulation frequencies.

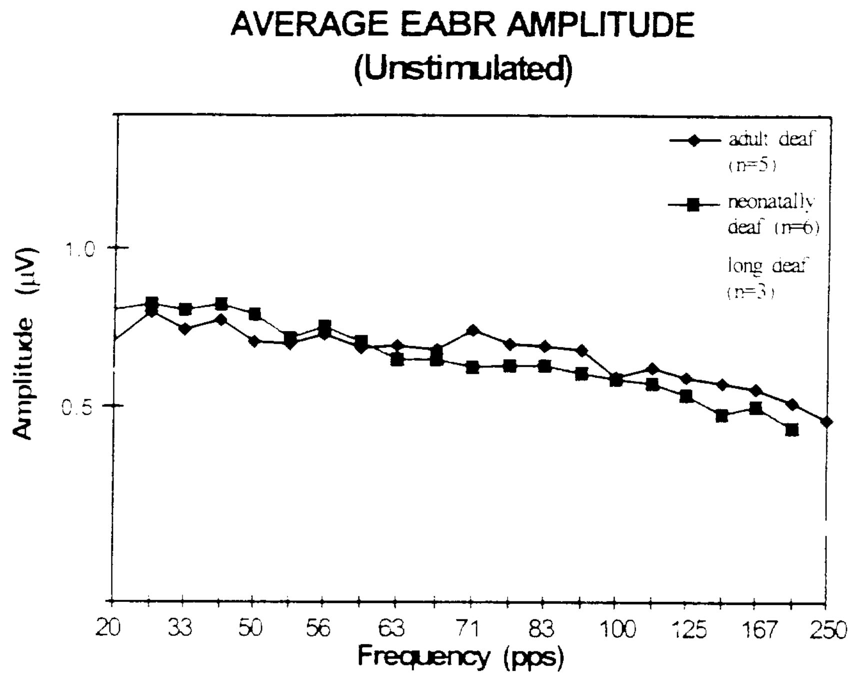

Figure 2. Average EABR wave III amplitudes for the three groups of unstimulated animals.

In Figure 3 the average EABR amplitudes are plotted to the relative maximum amplitudes for the individual (unstimulated) animals. This plot of *relative amplitude* allows direct comparison of frequency transfer functions. With the exception of some deviation for the frequencies 110-200 Hz in the long deafened animals, the three groups of experimental animals have very similar frequency transfer functions. Again, all groups show a decrease in response amplitude as the frequency of the stimulus increases.

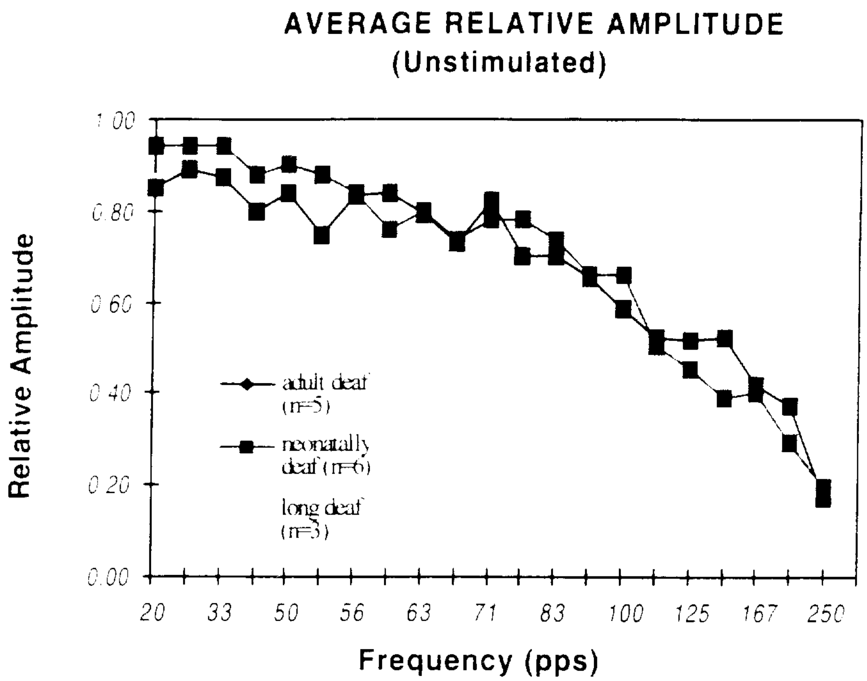

Figure 3. Average relative amplitude for the three groups of unstimulated animals as a function of stimulus frequency.

Effects of Chronic Stimulation

To evaluate the effects of chronic electrical stimulation on temporal resolution EABR measurements were repeated following stimulation for periods of 3 to 6 months. Figure 4 (a-c) shows the absolute amplitude data for the three groups of animals, recorded in response to stimulation via the chronically stimulated electrodes in each individual animal. Length of chronic electrical stimulation at the time of these most recent recordings is given in Table 1 for each animal. Similar to their unstimulated conditions, all animals show a decrease in EABR wave III amplitude for increasing stimulation frequencies.

Figure 5 illustrates the average amplitude for the three groups of stimulated animals. Neonatally deafened animals have consistently greater amplitudes than either the adult or long deafened groups. More importantly, the transfer functions appear to differ for each of the groups.

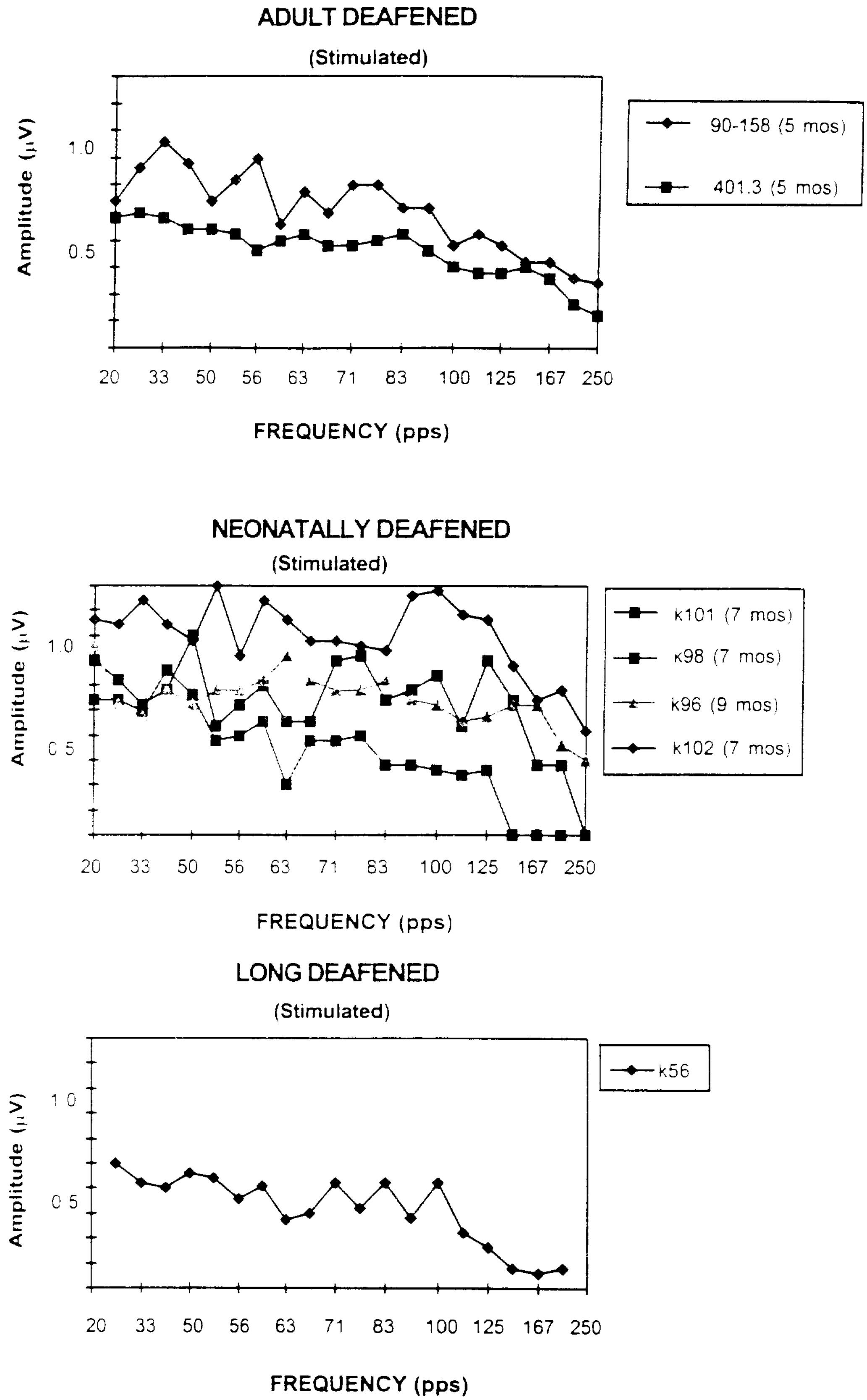

Figure 4. Individual absolute EABR wave III amplitudes for varying stimulation frequencies are presented for three groups of chronically stimulated animals.

In order to better compare and examine differences in the frequency transfer functions, the values were calculated again as percent of maximum or relative amplitude.

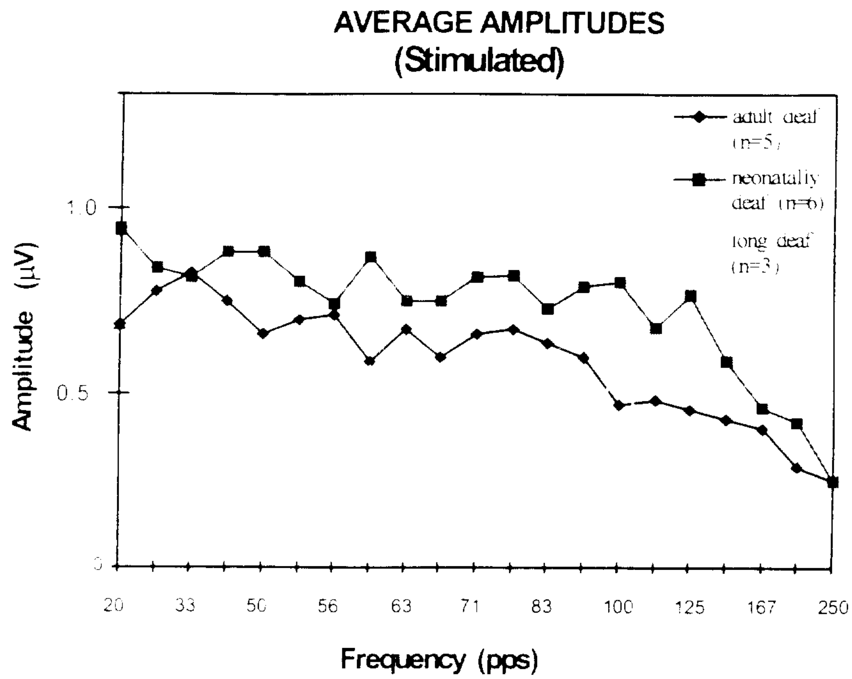

Figure 5. Average EABR wave III amplitude for varying stimulation frequencies following chronic electrical stimulation.

Figure 6 shows the average relative amplitudes for the 3 groups of stimulated animals as compared to the average values for all unstimulated animals. Long deafened animals exhibit a marked decrease in temporal resolution above stimulus frequencies of 100 pps. by comparison neonatally deafened animals appear to maintain better temporal resolution for frequencies above 125 pps. Adult deafened animals have frequency transfer functions which appear to be very similar to those of unstimulated animals.

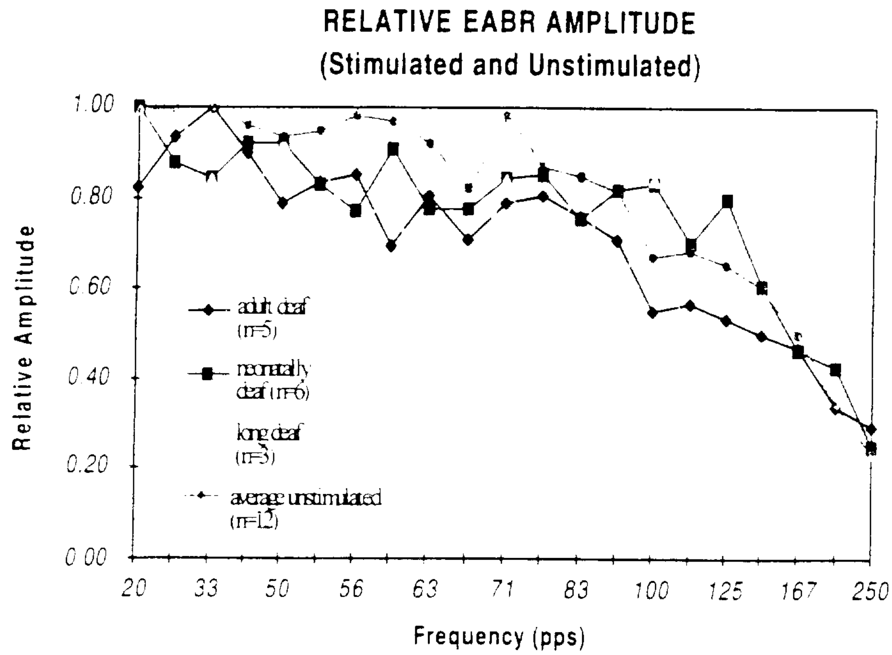

Figure 6. Averaged relative EABR wave III amplitudes for varying stimulation frequencies for the three groups of stimulated and unstimulated animals.

Comparisons of Unstimulated and Stimulated Conditions

Figure 7 again plots the EABR wave III average relative amplitudes as a function of frequency, this time comparing the stimulated and unstimulated conditions for each of the three groups of animals. The responses from the adult deafened animals, following several months of stimulation appear unchanged. However, since final measurements have been made in only 2 animals to date, these data are considered preliminary. Data from the neonatally deafened group show an increase in temporal resolution after chronic electrical stimulation as indicated by a consistent increase in relative response amplitude for stimulus frequencies of about 90 up to about 150pps. The data for the single long deafened, chronically stimulated cat shows a marked difference from initial average data for this group again (for frequencies of about 90 to 150 pps), but these data are obviously too limited at present to speculate about their significance.

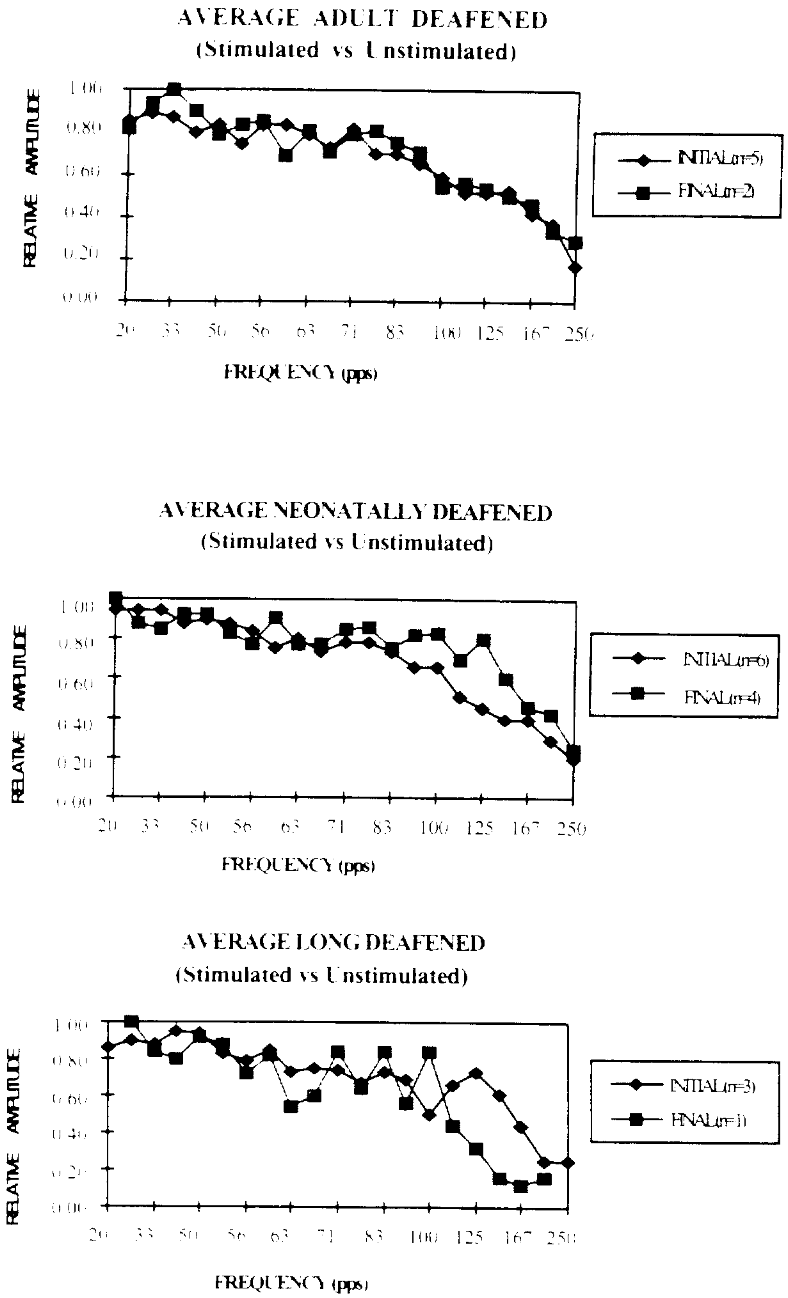

Figure 7. EABR wave III average relative amplitudes as a function of frequency plotted for the unstimulated for the unstimulated vs. stimulated conditions in the three experimental groups.

SUMMARY/DISCUSSION

Recent increases in the stimulation pulse rates in signals delivered by cochlear implant speech processors have resulted in substantial improvements in speech recognition of cochlear implant subjects. However, performance still varies considerably across individuals. A number of variables have been suggested which may contribute to these differences including the ability of auditory neurons to follow higher frequency pulse rates, i.e. the temporal resolving capacity of the central auditory system.

The main objective of the work presented in this QPR was to evaluate the frequency following capacity of the electrically evoked auditory brainstem response (EABR) as a non-invasive method of assessing temporal resolution. The ability to assess quantitatively responses evoked from the central auditory system could provide information on the temporal cues to the auditory system of the cochlear implant subject. Such a measure would be useful in predicting the performance of individual subjects and also in monitoring changes in temporal resolution over time.

In this QPR we have reported on differences in EABR frequency transfer function between three animal models of deafness. More specifically, the EABR response amplitudes to pulse series of increasing frequency were recorded and the resulting frequency transfer functions plotted. The amplitude of wave III was measured because it is the most robust and the least variable response to electrical stimulation. Because the response of EABR wave III occurs at approximately 2.0 ms it is assumed that it is generated by neurons central to the auditory nerve and, therefore, reflects temporal resolution of the central auditory system.

For all animals the amplitude of wave III decreased as the stimulation frequency increased. This finding was expected since it is well known that the EABR amplitude decreases with increasing stimulus repetition rate for acoustic (Thornton and Coleman, 1975, Electroencephalography and Clinical Neurophysiology, 39: 399-406) and electrical (Tykocinski et al., 1995, Hearing Research, 83: 124-142) signals. The absolute amplitudes varied depending on the animal model assessed. Although only limited data are available at present for the long deafened cats, their average absolute amplitude appears to be reduced as compared to either the adult deafened or the neonatally deafened animals. As reported previously (QPR #9 for this Contract, see Table 1) these long deafened cats also exhibit severe degeneration of the spiral ganglion (mean survival 12%, n=7) and cochlear nuclei (Lustig et al., 1994, Hearing Res., 74: 29-37). Thus, these EABR findings are interpreted as suggesting that a reduced population of responding neurons results in a reduced EABR response amplitude.

To examine and compare the frequency transfer functions between the groups of animals the data were replotted as relative amplitudes. The relative amplitudes allow comparisons of the frequency transfer functions regardless of the differences in absolute amplitudes between the groups. Plotted as average relative amplitudes for the three groups of unstimulated animals the frequency transfer functions were not significantly different. Thus, differences between the groups of unstimulated animals, such as previous acoustic experience, duration of deafness and/or expected cell survival, do not appear to influence temporal resolution.

In contrast, consistent differences in frequency transfer functions are observed in the between the two groups of chronically stimulated animals. The averaged data of the stimulated adult deafened cats show no change in temporal resolution following several months of chronic stimulation as compared to the unstimulated group of animals. Although the data are still preliminary, these results suggest that chronic electrical stimulation does not influence temporal resolution in animals deafened as adults. In contrast, chronic electrical stimulation appears to affect the temporal resolution of neonatally deafened animals. Although some variability is noted among the neonatally deafened animals, the temporal resolution of the central auditory nervous system in this group is higher than either the unstimulated animals or the stimulated adult animals. That is, the amplitude of the EABR diminishes at a much higher frequency in the chronically stimulated neonatally deafened group. The mechanism(s) responsible for this change in temporal resolution are unclear. However, since the neonatally deafened animals received electrical stimulation at a much younger age and as the intial input to the developing auditory system it seems likely that critical periods might play an important role in the differences seen between these animals and the adult deafened group. There is considerable evidence in other developing sensory systems that input activity, especially synchronized activity, exerts a powerful influence on the developing central nervous system. Thus we hypothesize that electrical stimulation in the developing auditory system may more effectively reinforce (entrain) excitatory central auditory connections, increasing synaptic efficiency and leading to the improved temporal resolution observed in the frequency transfer functions. Moreover, such effects may be much more limited in adult animals with normal acoustic input during development and prior to stimulation.

The data from the long deafened animals are too preliminary to draw a conclusion at this time. However, it is hypothesized that electrical stimulation, following long term auditory deprivation, does not significantly alter temporal resolution. Further, the extent to which chronic electrical stimulation can effectively alter the central auditory system is dependent upon developmental state.

WORK FOR NEXT QUARTER

1.) In the next quarter we will continue evaluating the EABRs of unstimulated and stimulated animals. Final EABR recordings will be made from 5 chronically stimulated animals (2 adult deafened, 2 neonatally deafened and 1 long deafened).

2.) The EABR frequency transfer functions will be compared to the average single neuron recordings made in the inferior colliculus.

3.) Electrically evoked compound action potentials (ECAPs), recorded from intracochlear electrodes, will be analyzed and compared to the EABR data.

4.) Morphological data from animals studied to date will be compiled and analyzed.