Tenth Quarterly Progress Report
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The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

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1   Introduction

The purpose of this contract is to explore issues involving the transfer of information from implantable auditory prostheses to the central nervous system with emphasis on how the auditory nerve encodes electric stimuli. Our investigation is being pursued along multiple parallel tracks and includes the use of animal experiments and computer model simulations to:

1. Characterize fundamental spatial and temporal properties of intra-cochlear stimulation of the mammalian auditory nerve.

2. Evaluate the use of novel stimuli and electrode arrays.

3. Evaluate proposed enhancements in animals with a partially degenerated auditory nerve.

In the Seventh Quarterly Progress Report (Matsuoka et al., 1998) we described in some detail the auditory nerve's response to constant-amplitude pulse trains from a series of animal experiments. In the Fourth Quarterly Progress Report (Abbas et al., 1997b), we presented preliminary data on amplitude modulation along with measurements of two-pulse refractory properties. We have now collected and analyzed data from a series of ten animals, some deafened immediately prior to the acute experimental session and others deafened for periods up to several months prior to data collection. This report focuses on the results from those experiments.

2   Summary of activities in the tenth quarter

In our tenth quarter (January 1999 through March 1999), the following activities related to this contract were completed:

- Continued noise-deafening of guinea pigs to be used in studies of chronically deafened and neurally degenerated animals.

- Conducted electrophysiological recordings on nine guinea pigs. Experiments included the use of amplitude modulated stimuli (reported in this QPR) as well as experiments manipulating stimulus waveform and constant amplitude pulse trains.

- Attended the 1999 Midwinter Meeting of the Association for Research in Otolaryngology and gave three podium presentations related to our contract work (see Appendix for details).

- Hosted a joint visit with consultants Blake Wilson and Don Eddington in which we reviewed our results and discussed both implications and future experiments.

- A manuscript describing pseudospontaneous activity was published in the January, 1999 edition of Hearing Research.

- A manuscript on single-unit responses was published in the April, 1999 edition of Hearing Research. This manuscript details all the single-fiber data collected using monopolar, monophasic stimulation (see Appendix).

- Revisions were completed on an additional manuscript regarding a phenomenological model of the EAP response, submitted to Hearing Research.

- Completed a series of model simulations of responses to "conditioned" and "unconditioned" sinusoidally amplitude modulated pulse trains.

3 Compound action potential in response to amplitude modulated pulse trains

3.1 Background

The electrically evoked compound action potential (EAP) provides a means of assessing the temporal response patterns of the auditory nerve in cochlear implant patients and experimental animals. Responses to pulse trains demonstrate refractory effects similar to those observed in a two-pulse, forward-masking paradigm (e.g., Brown et al., 1990; Abbas et al., 1997b). Unlike that paradigm, pulse trains can reveal more long-term effects that produce complex response patterns dependent on interpulse interval and stimulus level (Wilson et al., 1995; Matsuoka et al., 1998).

Responses to amplitude-modulated pulse trains are particularly appropriate for simulating the stimulus protocols used in many cochlear implants (such as CIS-type strategies). EAP measures from both humans and experimental animals demonstrate limitations in the ability of the auditory nerve to accurately encode certain stimulus patterns (Wilson et al., 1995; Matsuoka et al., 1998). They also generally show across-subject variation, presumably due to different patterns of nerve-fiber survival.

We investigated the response patterns to modulated pulse trains in both acutely deafened guinea pigs and in guinea pigs with long-term deafened ears. We sought to assess temporal response properties using a wide range of stimulus parameters in subjects with both intact fiber populations as well as in animals with neural degeneration. Assuming that neural degeneration secondary to deafening results in degraded temporal responses, our long-term deafened preparations may provide a suitable model for the typical implanted human auditory nerve. In contrast, the acutely deafened animals may provide a "best case" for neural representation of pulse train stimuli. In this report we concentrate on the general properties among the responses from both of these experimental groups. When more complete histological data is available, we will report on variations in response properties that may be related to degree and type of neural survival.

3.2   Methods

Five adult guinea pigs (labeled G89, G91, G92, G93, and G95) comprised the group with degeneration of the auditory nerve. Recordings were also made from five adult guinea pigs (labeled G54, G56, G65, G67 and G68) where there was no prior acoustic treatment. Each animal in the first group was anesthetized with ketamine and exposed to 115 dB SPL noise for periods of 2 hours. Their hearing was assessed using acoustic ABR 1-2 weeks after exposure and each had greater than 60 dB of hearing loss at frequencies above 1 kHz. These five animals survived at least 6-12 weeks before the electrophysiological recording session and subsequent sacrifice for histological evaluation. On the day of recordings, animals from both groups were deafened with intracochlear infusion of Neomycin. Recordings were made using a ball electrode placed on the auditory nerve. Monopolar stimulation was provided by a ball electrode placed in basal scala tympani via the round window. All stimulus pulses were biphasic (40 μs/phase). Anodic-first and cathodic-first biphasic pulse trains were presented in interleaved trains, enabling us to examine the effects of the starting phase. In some cases, however, we analyzed the summed response of the two stimulus polarities in order to effect stimulus artifact reduction. In most cases, interpulse interval (IPI) was 1 ms; pulse train duration was at least 150 ms. Modulation frequency, modulation depth, and stimulus level were systematically varied to assess their effects. In one subject (G67), higher pulse rates (IPI=0.2 ms) were employed to study higher modulation rates.

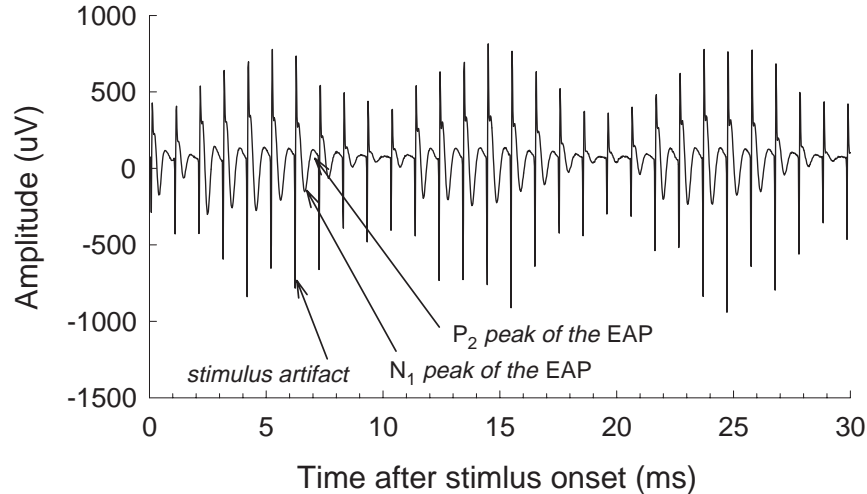Typical recorded responses to a modulated pulse train (100 Hz, 50%

Figure 1: Averaged EAP waveform in response to the first 30 ms of a pulse train. Responses to both cathodic- first and anodic-first pulse trains are averaged. The residual stimulus artifact is evident at one millisecond intervals. The EAP in response to each pulse is observed after each stimulus. Response amplitude is measured from the initial negative peak to the following positive peak as indicated.

modulation) are shown in Figure 1. Arrows point out the remaining stimulus artifact in this summed trace (sum of two polarities), as well as the N1 and P2 peaks of the EAP. EAP amplitude was computed by the voltage difference between N1 and P2.

Figure 2 shows EAP amplitudes in response to an amplitude-modulated pulse train. The periodic variation reflects variations in the stimulus; a transient effect can also be seen in the first 50 ms. A simple method of quantifying response modulation – the difference between maximum and minimum EAP amplitude – was computed over a period of 80 ms beginning 50 ms after stimulus onset in order to avoid transient effects.

3.3   Results

3.3.1   Effect of modulation depth

Figure 3 (left column) plots responses over a 50 ms period to illustrate details of the EAP amplitude variations. For no modulation, the response
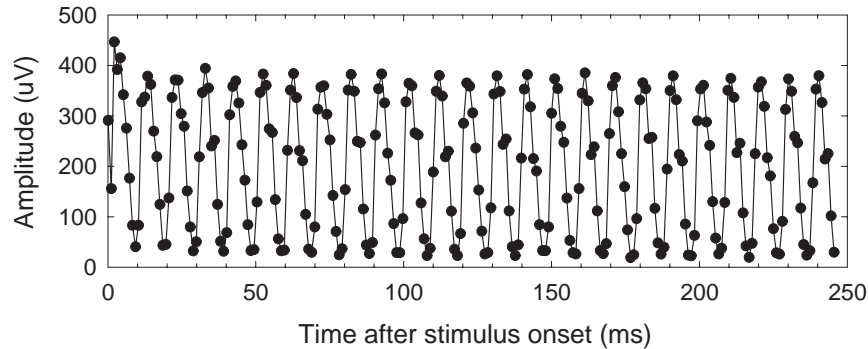
Figure 2: The measured amplitude of response to each pulse train is plotted as a function of time after stimulus onset for a sinusoidally modulated 250-ms pulse train with a interpulse interval of 1 ms. Responses to alternate stimulus polarities are summed.

is constant. For 1% modulation, some response variation is evident. As modulation depth increases, an approximately sinusoidal response pattern emerges. At high modulation depths, the response shows larger variations but also shows evidence of distortion. We can quantify the degree of response distortion using spectral analysis of the amplitude vs time signals. Figure 3 (right column) illustrates FFT amplitude components for the data in the left column. As modulation depth increases, there is a monotonic increase in the component of the response at the modulation frequency (here, 100 Hz). At the highest modulation depths (10% and 50%), there is considerable harmonic distortion, as well as a large increase in the DC component.

Similar effects are seen in recordings from animal G94 in Figure 4. Plots of the response amplitude across time as well as the FFT amplitude components are shown at several modulation depths. There is a significant alternation in the response to constant amplitude pulse trains (0% modulation); as the modulation depth is increased the alternating pattern of response is supplanted by a pattern of amplitude variation synchronized to the modulating stimulus frequency. The high degree of response alternation to constant amplitude pulse trains is a characteristic seen consistently in the human cochlear implant recordings (Wilson et al., 1997) but has not been consistently observed in our animal work in cats and guinea pigs (Matsuoka et al, 1998). In subject G94, there is considerable distortion, evident in the appearance of a second peak in the time waveform as well as in the considerable harmonic distortion. While this animal showed a particularly high
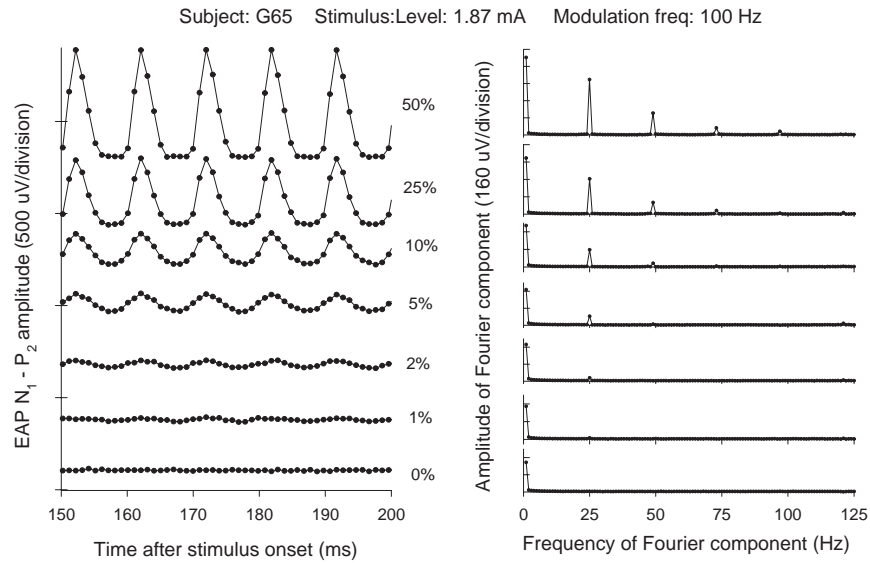
Figure 3: In the plots on the left, the response amplitude is plotted as a function of time after stimulus onset. The plot at right represent the FFT amplitude for the corresponding time waveforms on the left. The stimulus in each case is a 250-ms pulse train; only a limited region of the response is plotted here for clarity. Stimuli were biphasic pulses (40 μ/phase) with an IPI of 1 ms and mean level of 1.87 mA. Modulation frequency was 100 Hz. Each pair of graphs shows data for a different modulation depth as indicated. Responses to alternate stimulus polarities are summed.

degree of distortion and is in the chronically deafened group, it is not yet clear that this is a characteristic of ears with significant degeneration. In fact, other animals in this group did not show the same degree of distortion. Further recordings and also results of histological analysis will help to determine the degree to which such effects (both response alternation and distortion) may be correlated with nerve degeneration.

We quantified the degree of distortion by summing the amplitude of the harmonic frequencies and dividing it by the sum of those amplitudes and that of the fundamental component. Figure 5 plots such data for cathodic-first pulses for several levels of pulse amplitude. These data reflect the general trend that we have observed in that, as modulation depth is increased, the degree of distortion also increases. The plot shows values for different overall stimulus level. As will be discussed in a later section, the distortion characteristics are also highly dependent on stimulus level.

3.3.2   Effect of stimulus polarity

Response modulation (maximum -minimum amplitude) is plotted as a function of modulation depth in Figure 6 for four animals. Data are plotted for the summed (cathodic-first + anodic-first) response, as well as for the responses to the two stimulus polarities measured separately (cathodic-first and anodic-first). These cases illustrate the general trend that cathodic-first stimuli resulted in greater response modulation and steeper growth with modulation depth than anodic-first stimuli. The trends for the summed response are similar to those for each polarity measured separately.

3.3.3   Effect of stimulus level

The effects of stimulus level were evaluated by plotting the response modulation (i.e., maximum-minimum amplitude) as a function of stimulus level with modulation depth as a parameter (Figure 7). Response amplitude increases with increasing level over a range of levels in all four examples shown. We generally observed a saturation at high stimulus levels. In some cases, we observe a clear decrease at high stimulus levels (e.g., G91, G67). Note that this decrease in response occurs despite the fact that stimulus modulation in terms of absolute level continues to increase. This pattern of behavior is consistent with the limited dynamic range of EAP response (Abbas et al., 1997a). Stimulus modulation around a stimulus level in the middle of the dynamic range would be expected to produce large response modulation. If
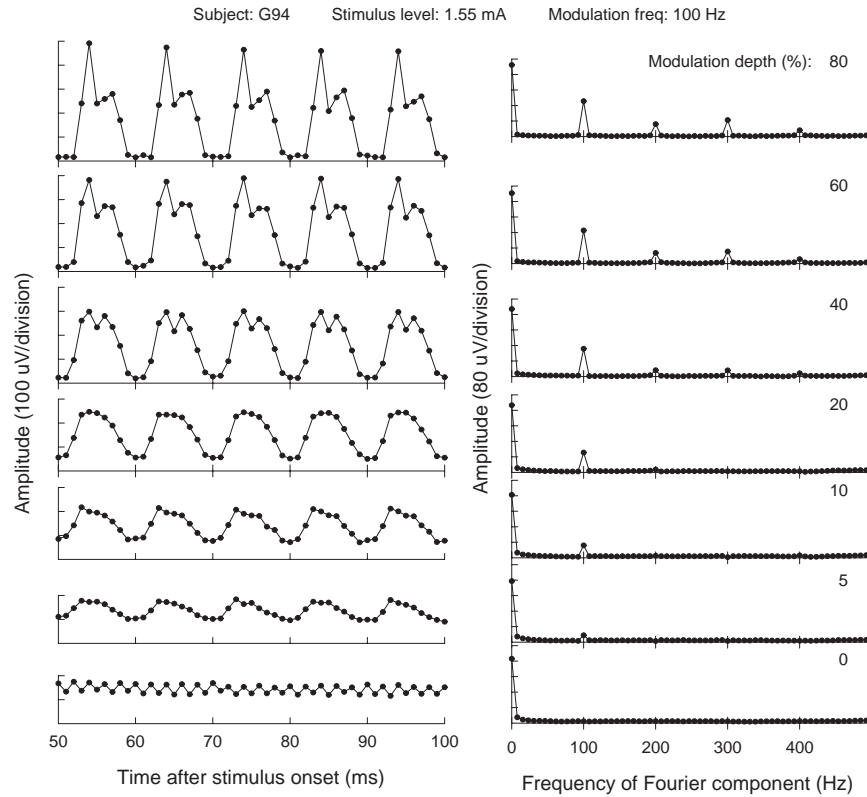
Figure 4: In the plots on the left, the response amplitude is plotted as a function of time after stimulus onset. The plot at right represent the FFT amplitude for the corresponding time waveforms on the left. Stimulus in each case is a 150-ms pulse train; only a limited region of the response is plotted here. Stimuli were biphasic pulses (40 μs/phase) with an IPI of 1 ms and level of 1.55 mA. Modulation frequency was 100 Hz. Each pair of graphs shows data for a different modulation depth as indicated. Cathodal-first stimulus.
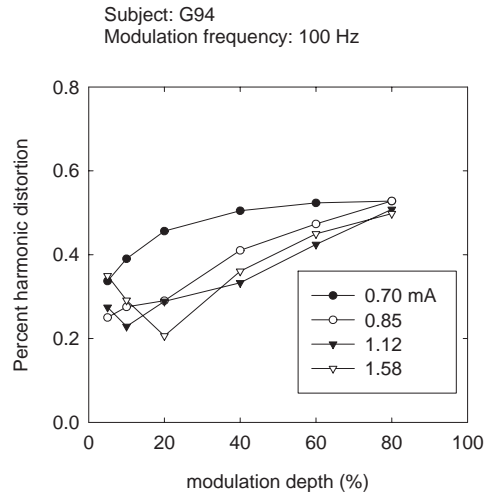
Figure 5: Percent harmonic distortion, observed in the EAP response to moduated pulse trains vs. modulation depth. Distortion was used using the Fourier components as illustrated in Figure 4. Parameter is stimulus level indicated in the legend.

stimulus level is near threshold or near EAP saturaton level (where the response growth is relatively shallow), then the expected response modulation would be less.

Figure 8 plots the percent distortion as a function of stimulus level for the same responses from which the data in Figure 7 were derived. At high stimulus levels, there is a general trend for distortion to increase with stimulus level. In some subjects we have observed a decrease in distortion with increasing level at low stimulus levels (e.g., G91, G67). We also attribute such behavior at least in part to the dynamic range of response as well as to refractory effects at high stimulus levels (Abbas et al., 1997a,b).

3.3.4   Effect of modulation frequency

Figure 9 plots the response amplitude as a function of modulation depth in four subjects for modulation frequencies 50, 100 and 200 Hz. The plots demonstrate the general trend seen in our data that the response modulation is greater at higher modulation frequencies. This effect may be attributed, in part, to neural refractory properties. At high modulation frequencies, the faster alternation in the stimulus level approaches that of the refractory
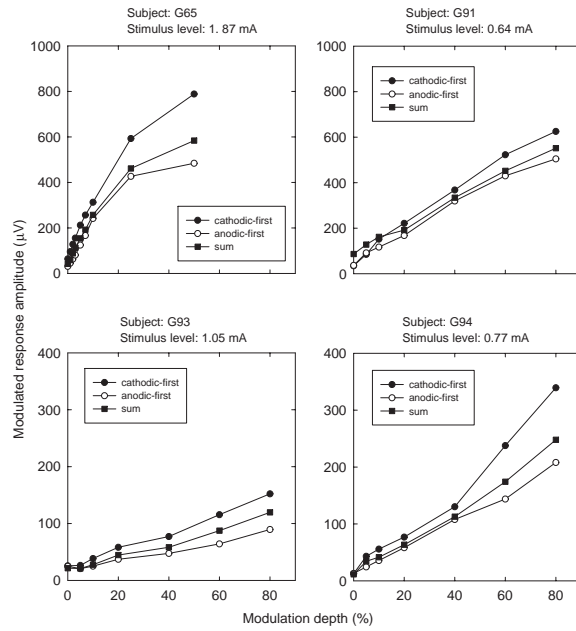
Figure 6: Effects of stimulus polarity. Response amplitude (maximum-minimum amplitude) is plotted as a function of modulation depth for four different experimental subjects. In each graph responses are plotted for both cathodic-first and anodic-first biphasic pulses as well as for the summed response measured from the average of the two.
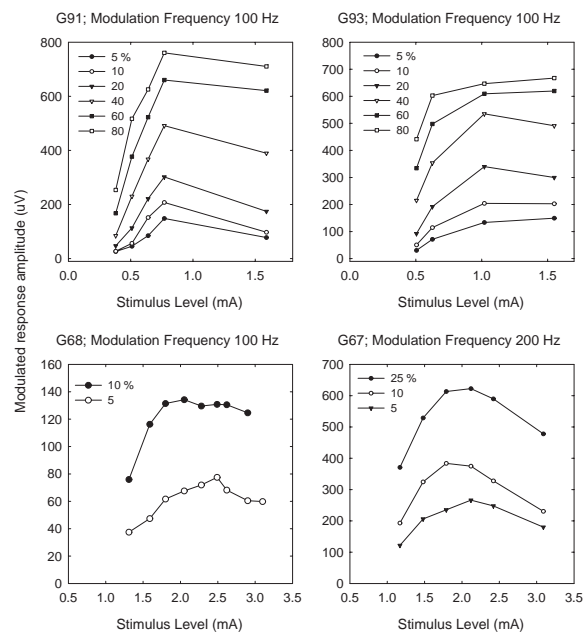
Figure 7: Effects of stimulus level. Response amplitude plotted as a function of stimulus level with modulation depth as a parameter. Data are plotted from four subjects, in each data for several modulation depths are shown.
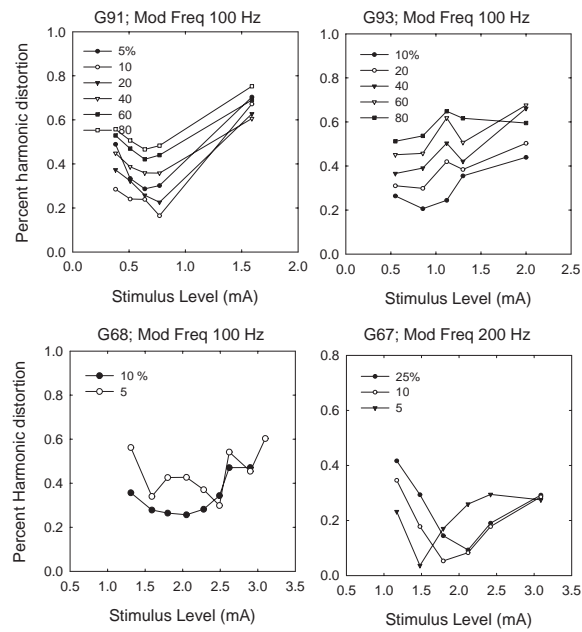
Figure 8: Percent harmonic distortion plotted as function of stimulus level with modulation depth a parameter. The percent distortion is calculated from the corresponding data plotted in Figure 7.
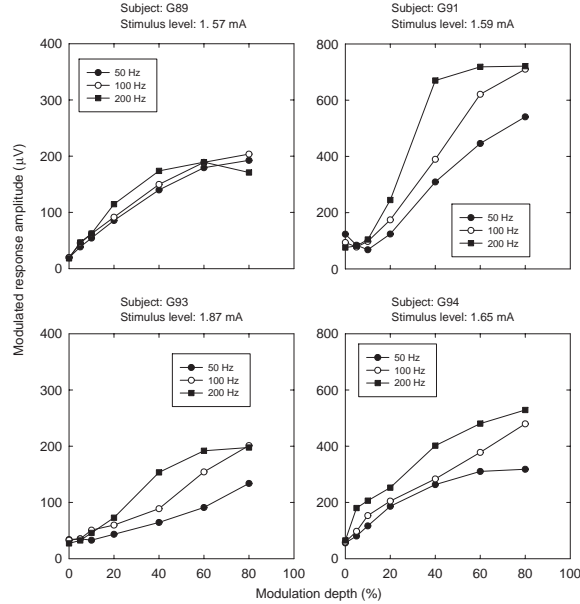
Figure 9: Effects of stimulus frequency. Modulated response amplitude is plotted as a function of modulation depth with modulation frequency as a parameter. Data from four subjects are plotted in the four graphs as indicated. Cathodal-first stimulus.

period, resulting in a greater alternation in the number of fibers capable of responding to each subsequent stimulus pulse. In addition we note that the growth of response modulation is greater at higher modulation frequencies, i.e., the growth of response is greater with increasing modulation depth for higher modulation frequencies.

In several subjects we have employed a wider range of modulation frequency. Figure 10 illustrates the response amplitudes plotted as a function of modulation frequency for one of these subjects. Modulation depth is the parameter. The plots demonstrate the general trend that we have observed; response modulation is greater at higher modulation frequencies, even when stimulus modulation depth is fixed.

To examine the effects of modulation frequencies higher than 400 Hz, we used higher pulses rates (IPI=0.2 ms) in one subject. Since there was considerable overlap in EAP responses to successive pulses of the train, a subtraction method was used to extract the response to each pulse (Wilson et al., 1995). For example, to determine the response to the nth pulse in
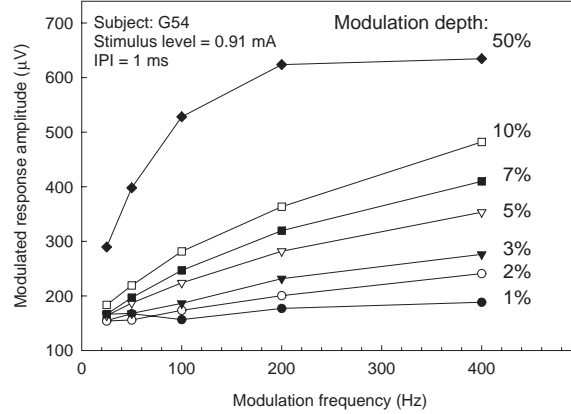
Figure 10: Response amplitude plotted as a function of modulation frequency, with modulation depth as a parameter. Responses to alternate stimulus polarities are summed.

the train, the response to $n-1$ pulses was subtracted from the response to n pulses. This method is time-consuming, so responses were measured over only one or two periods of the modulation waveform. An example showing the effect of changing modulation depth for a fixed modulation frequency is shown in Figure 11. The effect of changing modulation frequency for a fixed modulation depth is illustrated in Figure 12. Results are similar to those shown for lower pulse rates. Note that, by using the faster pulse rate, response modulation grows for modulation frequencies up to 1600 Hz.

3.4   Conclusions

The EAP response to electrical pulse trains is very sensitive to low levels of amplitude modulation. Stimulus modulations depths as low as 1% show evidence of response modulation. Also, over a range of modulation frequencies and depths, EAP amplitude accurately represents the modulated stimulus. There are, however, limitations in the representation of the signal as assessed with the EAP. Generally we observed lower response amplitude at extremes of stimulus level (Figure 7). We also have observed ranges of stimulation level and modulation depth where distortion is particularly high (Figures 5 and 8). Response modulation was also observed to be particularly sensitive to modulation frequency (Figures 9 and 10). At some stimulus levels, significant distortion was evident across the range of modulation depths.
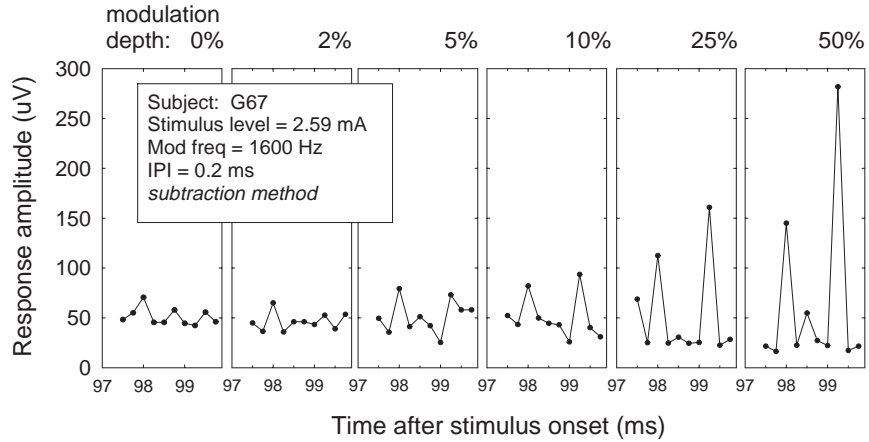
Figure 11: Response amplitude in response to pulse trains with IPI of 0.2 ms. Each panel represents response amplitude as function of time (indicated in time after stimulus onset) for a different modulation depth. Responses to alternate stimulus polarities are summed.
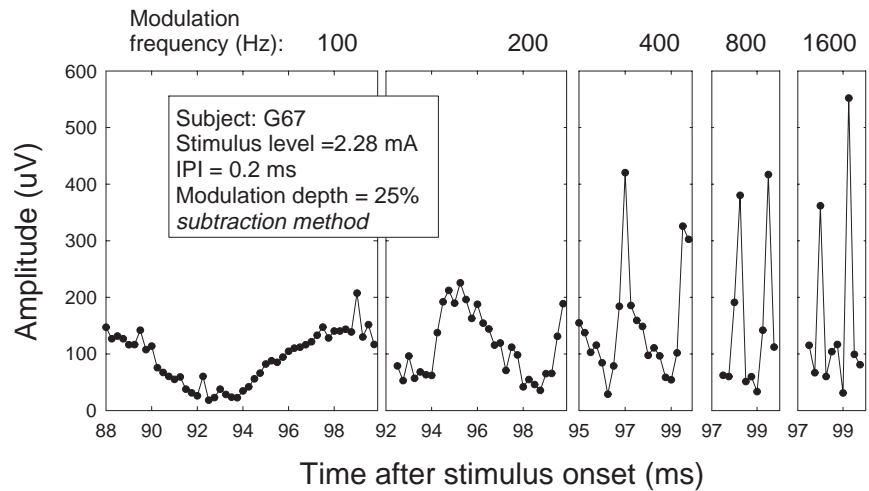

Figure 12: Modulation frequency effects in response to pulse trains with IPI of 0.2 ms. Each panel represents response amplitude as function of time (indicated in time after stimulus onset) for a different modulation frequency. Responses to alternate stimulus polarities are summed.

The effects of stimulus level and modulation frequency suggest that both the dynamic range of the EAP and the refractory properties may affect the degree of modulation and consequently the nerve's ability to encode pulse amplitude information.

The results are qualitatively similar to those measured in human implant users (Wilson et al., 1995) in that modulated response amplitudes show similar variations with modulation frequency and depth. A more detailed comparison of differences between responses in acutely deafened animals, long-term deafened animals and long-term deafened human cochlear implant users is warranted. Such an analysis may provide insight into the underlying mechanisms for these observed effects.

The trends reported here bring up the important issue of the degree to which the peripheral responses are relevant to human perception. One example may be the effects of modulation frequency as measured through the EAP where response modulation is a clearly increasing function of modulation frequency up to 400 Hz. By using high pulse rates we extended our measures in one animal and still observed increases up to 1600 Hz. Psychophysical data describing detection of such signals generally show the opposite effect: threshold modulation depth for detection increases with modulation frequency (Shannon, 1992) . This contrast between physiological and psychophysical data is consistent with a hypothesis that psychophysical performance on such temporal tasks may be limited by central neural mechanisms rather than peripheral properties.

A second example is the relevance of distortion on perception. The high degree of distortion observed under certain stimulus conditions (Figure 4) suggests that there may significant distortion of a complex signal (e.g. speech as seen in humans by Wilson et al., 1997). One may hypothesize that under such conditions perception may be impaired. Physiological data across a wide range of stimulus and nerve degeneration can suggest specific psychophysical experiments to test these hypotheses.

4   Plans for next quarter

- Continue to deafen ears of guinea pigs using a kanamycin and ethacrynic acid treatment as well as further EAP recordings on those subjects.

- Continue histological analysis of long-term deafened guinea pig ears.

- Begin single unit experiments on cats specifically investigating the

effects of pulse type and forward masking.

- Continue model development for a fiber population with a physiologic range of thresholds as determined by single-unit data.

References

[1] Abbas, P.J., Rubinstein, J.T., Miller, C.A. & Matsuoka, A.J. (1997a). First Quarterly Progress Report. The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation, NIH Contract N01-DC-6-2111.

[2] Abbas, P.J., Miller, C.A., Matsuoka, A.J. & Rubinstein, J.T. (1997b). Fourth Quarterly Progress Report. The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation, NIH Contract N01-DC-6-2111.

[3] Brown, C.J., Abbas, P.J., & Gantz, B. (1990). Electrically evoked whole-nerve action potentials I. Data from Symbion cochlear implant users. J. Acoust. Soc. Am., 88, 1385-1.

[4] Matsuoka, A.J., Abbas, P.J., Rubinstein, J.T. and Miller, C.A.(1998). Seventh Quarterly Progress Report. The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation, NIH Contract N01-DC-6-2111.

[5] Shannon, R.V. (1992). Temporal modulation transfer function in patients with cochlear implants. J. Acoust. Soc. Am., 91, 2156-2164.

[6] Wilson, B.S., Finley, C.C., Lawson, D.T. and Zerbi, M. (1995). Eleventh Quarterly Progress Report, Speech Processors for Auditory Prostheses, NIH Contract N01-2-2401.391.

[7] Wilson, B.S., Finley, C.C., Lawson, D.T., & Zerbi, M. (1997). Temporal representations with cochlear implants. American Journal of Otology, 18:S30-S34.

5   Presentations and publications

5.1   Presentations given at the 1999 ARO Meeting

- Matsuoka, A.J., Abbas, P.J., Rubinstein, and Miller, C.A. (1999) Compound action potential responses to electrical constant-amplitude

pulse trains. Abstract #29, Association for Research in Otolaryngology Midwinter Meeting 22, St. Petersburg Beach, FL.

- Miller, C.A., Abbas, P.J., Rubinstein, J.T., Robinson, B.K., and Matsuoka, A.J. (1999) Intracochlear electrical excitation of single auditory nerve fibers: Insights into modes of neural excitation and recruitment. Abstract #30, Association for Research in Otolaryngology Midwinter Meeting 22, St. Petersburg Beach, FL

- Rubinstein, J.T., Miller, C.A., and Abbas, P.J. (1999) Emulating physiologic firing patterns of auditory neurons with electrical stimulation. Abstract #31, Association for Research in Otolaryngology Midwinter Meeting 22, St. Petersburg Beach, FL.

5.2   Manuscripts Published in this quarter

- Miller, C.A., Abbas, P.J., Robinson, B.K., Rubinstein, J.T., and Matsuoka, A.J. (1999) Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophasic stimulation. Hear. Res. 130, 197-218.

- Rubinstein, J.T., Wilson, B.S., Finley, C.C. and Abbas, P.J. (1999). Pseudospontaneous activity: stochastic independence of auditory nerve fibers with electrical stimulation. Hear. Res., 127, 108-118.