Neural Prosthesis Program Contract N01-DC-02-1006

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation

Final Report

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I. Introduction

The overall goal of work proposed in this contract is to understand the factors that influence the spatial (spectral) and temporal distribution of neural activity across the tonotopic organization in the central auditory system evoked by multi-channel auditory prostheses (APs). Contemporary human APs have several electrical contacts distributed along the cochlear spiral. Each of these contacts is activated with unique patterns of pulse trains, which are thought to excite restricted and unique populations of auditory nerve fibers. Individual pulse amplitudes within a train are modulated by band-pass filtered ambient sounds, which have been processed by implant processors. Previous studies have indicated that contemporary devices are adequate to allow open-set speech reception in some AP users, but that their spatial resolution is not yet optimal. The proposed experiments seek to improve the spatial and temporal resolution of APs by improving our understanding of the factors that govern them. Multi-channel intracochlear stimulation delivered via multi-channel intracochlear electrodes, which accurately model those used in human APs, is used to examine these factors in anesthetized and un-anesthetized deaf animal models. These experiments closely simulate AP use, implementing multi-channel intracochlear electrical stimulation (ICES) using progressively more complex signals. Successful completion of these experiments will allow APs to activate the human auditory system with greater spatial and temporal resolution and to provide better speech reception to their users.

[This text has been excerpted and modified from the original contract proposal.]

A. Overview

This final report is organized largely according to the specific goals described in the contract proposal, which are paraphrased below in Section B. It briefly describes our work developing and characterizing a cochlear implant designed specifically for studies using animal models. Following this, it describes results of several physiological studies we have undertaken, each with the goal of improving our understanding differences in information processing carried out by the auditory system in two distinctly different paradigms -- processing of natural sounds that have been presented to the normal hearing ear, and processing of electrical stimuli presented to the deaf ear by a cochlear implant. Understanding these differences must provide new insights into optimizing the processing of electrical stimuli. Following this is a brief comparison of responses to acoustic stimulation measured in awake and anesthetized animals. The report concludes with a list of publications and public presentations of work supported by this contract.

B. Specific Objectives 1-5

The specific objectives of this contract, listed below in their original order, are paraphrased from the contract proposal:

> 1) Implement and document methods of ICES that will allow activation of multiple (at least 4) independent intracochlear stimulation channels. When activated individually, these channels will excite a tonotopically appropriate regions of the inferior colliculus (IC), which do not overlap with those excited by adjacent channels at stimulus intensities up to 6 dB above threshold.

2) Using these stimulation channels, study the spatial interactions among ICES channels by measuring the distribution of inhibition and facilitation evoked by multi-channel ICES across the tonotopic organization of the IC. Vary stimulus intensity and intracochlear channel-separation in order to vary the magnitude of the interactions. Compare these interactions with those evoked by multi-component acoustic stimulation in a normal hearing animal.

3) In addition to spatial interactions, determine the magnitude and nature of the temporal interactions within and between AP channels by measuring the magnitude and time course of simultaneous and forward masking stimuli and probe stimuli using single and multi-channel ICES.

4) Employ the most commonly used parameters, which are adjusted in AP "fitting" procedures, to maximize the differences between central nervous system representations of temporally complex signals, including speech stimuli processed by AP speech processors. Among these parameters are the effects of adjustments of threshold, dynamic range and most importantly compression. The speech stimuli used will be standardized acoustic speech signals (taken from the Hillenbrand recordings), which have been processed by software implementations of commercial AP speech processors. They will be presented in isolation and in the presence of background noise in order to simulate more closely real-life AP use.

5) Initially these studies will be conducted in anesthetized animals. In later studies, examine the spatial and temporal interactions seen in the response of IC neurons of un-anesthetized animals and compare them with those seen in the IC of anesthetized animals.

C. Scope of completed anticipated and unanticipated issues addressed

In the original contract proposal we recognized that our research aims were ambitious. We also recognized that the focus of later experiments depended on the successful completion of earlier ones. And finally we acknowledged that we would be confronted by questions and issues that had to be addressed, but which were not anticipated at the time the proposal was written. Among the proposed objectives we have completed are: 1) We have manufactured a multichannel intracochlear electrode designed specifically for the guinea pig. 2) We have completed experiments examining the responses to simple electrical signals (single pulses and unmodulated pulse trains) and moderately complex electrical signals (SAM pulse trains). 3) We have completed experiments using simple acoustic signals in anesthetized and unanesthetized animals. 4) We have completed experiments using moderately complex acoustic signals (SAM tones and noise bands that vary in bandwidth). 5) We have completed experiments examining the interactions between two signals presented simultaneously on one channel. 6) We have completed experiments examining the interactions between two *non-simultaneous* acoustic channels using forward masking of simple signals and between two *non-simultaneous* electric stimulus channels using forward masking. In addition, we have conducted an examination of the interactions between simultaneously presented moderately complex signals (SAM tones and SAM pulse trains). This is a partial list of the progress we made on issues that we anticipated and proposed as objectives. Other issues that were unanticipated but nevertheless had to be addressed were: 1) Study of channel interactions between two electrical signals that were co-incident, i.e., current steering and the effects of variations in remote current fraction (RCF), and 2) study of the effects of stimulus waveform (biphasic vs. pseudomonophasic pulses) on the central representation of simple electrical signals. A summary of the results of these studies is presented below.

II. Development and characterization of a cochlear implant for the guinea pig – Objective 1

A. Development of cochlear implant

We have developed a cochlear implant (CI) for the guinea pig that is designed to closely model contemporary cochlear implants used in humans. This implant comprises multiple (up to sixteen) platinum/iridium wires, terminating in balls or flattened disks, embedded in a form-fitting silicone elastomer carrier. This non-conductive carrier displaces conductive perilymph from the scala tympani, reducing current required for stimulation of the auditory nerve, lowering stimulus threshold and increasing stimulus selectivity. When the implant is inserted into the scala tympani, the contacts are normally positioned in close proximity to the habenula. We have used two design generations of this implant to conduct neurophysiology experiments in the guinea pig. Using this cochlear implant with bipolar current pulse stimulation, we are able to selectively elicit neuronal responses from more than four non-overlapping regions of the inferior colliculus. A manuscript describing development and fabrication techniques used to construct these cochlear implants for guinea pigs, as well as for cats, has been submitted to the Journal of Neuroscience Methods (Rebscher et al., submitted). During the contract period, we distributed several of these implants to other research laboratories in the U.S. and in Europe.

Recommendation for future work: Using the current (second) generation of this cochlear implant, the current required for stimulation of the auditory nerve can be somewhat reduced and the specificity of monopolar stimulation can be increased by applying a slight torsion after the implant is inserted into the scala tympani. This torsion effectively repositions stimulating contacts, placing them somewhat closer to the the modiolus and thereby reducing stimulus threshold. We recommend that the next generation of these devices be designed to position stimulating contacts close to the modiolus without post-insertion torsion.

B. Comparative physiological studies using UCSF CI, manually-positioned ball electrodes, and a commercially-available CI designed for animal experiments

To evaluate the performance of our cochlear implant, we conducted a series of studies that compared spatial distribution of activity in the inferior colliculus elicited by stimulation using the implant with responses elicited by: 1) acoustic stimulation of the cochlea, 2) electrical stimulation of the cochlea using manually-positioned ball electrodes, and 3) electrical stimulation of the cochlea using a commercially-available banded electrode produced for animal research (available from Cochlear Ltd.). Results of these studies have been published (Snyder et al. 2004; Snyder et al., submitted; Snyder & Bonham, 2007) and they indicate that responses elicited using either this electrode or manually-positioned ball electrodes with bipolar stimulation could be as focal as or more focal than responses elicited using pure-tone acoustic stimulation. In contrast, responses elicited by the commercially-available electrodes were broad regardless of the stimulation mode. This comparison highlights the significant advantage of our implant over commercially available electrodes in specificity of stimulation, which is probably due to their smaller contact size, the space-filling nature of the carrier, and the more favorable placement of stimulating contacts nearer the excitable neural elements. Our implant also manifests a clear advantage over manually-positioned ball electrodes in ease of application and in the number of discrete stimulating contacts that can be simultaneously inserted. A manuscript describing the results of these studies has been submitted for publication to Hearing Research (Snyder et al.).

III. Physiology studies using acoustic or electrical stimulation – Objectives 2, 3, and 4

Responses of the auditory nervous system to acoustic or electric stimulation of the cochlea have both spatial and temporal characteristics. Studies of response to cochlear stimulation therefore necessarily generate observations that address questions within the scope of both specific objectives 2, 3, and 4. Descriptions and results of studies addressing each of these objectives are listed below according to the focus of the study, rather than by division between spatial and temporal aspects of responses. The studies described below are however divided between studies using single-pulse stimulation, which tend to emphasize spatial rather than temporal aspects of interaction between stimulus channels, and studies using stimuli of extended duration (acoustic tones or constant-level electrical pulse trains).

A. Studies examining response to single electrical pulses

1. Comparison of responses using mono-, bi-, and tri-polar stimulation modes

We characterized inferior colliculus responses elicited by electrical stimulation of the cochlea in each of three stimulation modes: 1) monopolar, in which current is applied to the cochlea via a single intracochlear electrode and the return path is through an extracochlear electrode, 2) bipolar, in which current is applied via a single intracochlear electrode and the return path is via a second single intracochlear electrode, and 3) tripolar, in which current is applied via an intracochlear electrode, and half that current is returned via each of two other, usually adjacent, intracochlear electrodes. Our observations of monopolar and bipolar responses were consistent with similar measurements from our laboratory in a cat model: responses to monopolar stimulation were broadly distributed along the IC tonotopic axis and exhibited poor dynamic range, but had low thresholds, while responses to bipolar stimulation were more focal, had greater dynamic range, but had higher thresholds. In a small number of instances using monopolar stimulation we did see focal responses and larger dynamic range, which suggests that animal to animal variation, perhaps in cochlear geometry or electrode placement, though this is unknown, plays a significant role in determining the response to monopolar electrical stimulation. Measurements of the distributed response to tripolar stimulation indicated that these responses were moderately more spatially restricted than bipolar responses, and response thresholds for tripolar stimulation were almost uniformly higher than bipolar thresholds. While monopolar stimulation is most frequently used in clinically applied speech processing strategies, perception of monopolar stimulation in humans appears to be focal (i.e., the perception of stimulation of a single CI electrode is more tone-like than like broadband noise). For most of our studies in the guinea pig we used focal bipolar stimulation as a model of focal monopolar stimulation in humans.

2. Studies examining the effect of electrode separation

In these studies we examined the effect of electrode separation of the two electrodes comprising a bipolar electrode pair. In symmetric bipolar stimulation, an activating current pulse is applied to one electrode and the return path for the current is another intracochlear electrode. Following this activating pulse, a charge-balancing pulse of equal magnitude, but opposite polarity, is presented on the first electrode, while the current is again returned via the second electrode. This has the effect of presenting an equivalent activating pulse on the second (originally return) electrode. The distribution of activity along the IC tonotopic axis elicited by symmetric biphasic activation using broadly-spaced bipolar electrode pairs (>=1 mm separation) exhibited two peaks of activity, as well as two locations with low resp0nse thresholds. – one corresponding to the location of each of the electrodes in the bipolar pair. Activation using narrowly-spaced bipolar pairs did not exhibit similar peaks. This suggests that to achieve focal stimulation using symmetric biphasic pulses of bipolar electrode pairs requires that the two electrodes in each pair be within a characteristic distance of one another. It is possible, though we believe unlikely, that closer spacing of recording sites (recording site spacing was 100 microns) would have resolved two peaks.

3. Studies examining the effect of stimulus waveform

As described above, the charge-balancing phase creates a second point of stimulation within the cochlea when bipolar stimulation is used. One way to reduce the effect of stimulation by the charge-balancing phase is to reduce it's amplitude while extending it's duration to maintain charge balance. We examined profiles of responses along the IC tonotopic axis to “pseudomonophasic” pulse stimuli delivered to the cochlea using monopolar and bipolar stimulation modes. For bipolar stimulation using broadly-spaced bipolar pairs, response profiles exhibited a single peak, usually, but not always, corresponding to the location of the electrode that received the cathodic high-amplitude/short-phase-duration pulse. For bipolar stimulation using narrowly-spaced bipoles, the response profile was different depending on which of the two bipolar electrodes received the cathodic high-amplitude/short-phase-duration pulse. When the stimulus polarity was switched, the response profile changed slightly but significantly, indicating that pseudomonophasic pulses were able to stimulate spiral ganglion neurons in uniquely distinct, but probably overlapping, regions of the cochlea. For monopolar pseudomonophasic As expected, response thresholds increased dramatically and response profiles became significantly broader when the activating phase was applied to the extracochlear electrode. Our observation that distinct cochlear regions can be activated using pseudomonophasic pulses applied to a single bipolar electrode pair suggests that the number of perceptibly distinct stimuli may be increased by modification of the stimulus waveform for human CI users, for example, by application of a pseudomonophasic stimulation strategy.

4. Studies examining the effect of proportional current division (current steering)

The number of perceptibly different stimuli might also be increased by proportionally dividing a fixed stimulus current between two intracochlear channels to create “virtual” channels, and the effectiveness of this strategy has previously been demonstrated in human implant users. In this series of experiments, we characterized the physiological correlate of virtual-channel perception in the inferior colliculus. Using a monopolar stimulation strategy, we divided a fixed activating current between two intracochlear electrodes; the return path for this current was a single extracochlear electrode. In most cases, the profile of response along the IC tonotopic axis was broad and exhibited a narrow dynamic range, similar to monopolar stimulation using a single intracochlear electrode. In a small number of instances in which we had observed relatively narrowly distributed monopolar tuning, we were able to observe similarly narrow tuning when current was divided between monopolar electrodes, and the location of the strongest response gradually changed according to the proportional division of current. We interpret this observation as evidence of “virtual” channel stimulation in the guinea pig using monopolar stimulation.

As mentioned above, however, most responses to monopolar stimulation were too broad to reliably identify any peak of response along the tonotopic axis. We were reliably able to gradually shift the peak of response along the tonotopic axis by proportionally dividing current between bipolar electrode pairs using pseudomonophasic pulse stimuli. In some instances using monopolar stimulation, we observed that the peak of activity did not gradually shift along the tonotopic axis, but instead jumped from one location to another with an incremental change in the proportion of current delivered to each electrode. We interpret this observation as evidence of the absence of virtual channel stimulation in these instances, and suggest that this phenomenon may be responsible for the lack of virtual channel percepts experienced by some implant users. Simple modeling of potential fields suggest that this effect may occur when CI electrodes are positioned closer than a characteristic distance to responsive elements of spiral ganglion neurons.

5. Studies examining the effect of varying the remote current fraction (RCF)

As mentioned earlier, response thresholds for monopolar stimulation are low, while specificity of monopolar stimulation is relatively poor. In contrast, specificity of tripolar stimulation is good, while thresholds are significantly higher than those for monopolar stimulation. Focal stimulation accompanied by low thresholds might be characterized as the optimal configuration. In these studies, we investigated the possibility that response thresholds for tripolar stimulation might be lowered by using an extracochlear electrode as the return path for a part of the current applied to the active (center) electrode of the tripolar electrode set. (An alternative interpretation of this paradigm is that the precision of monopolar stimulation might be increased by restricting the potential field by returning a part of the stimulating current on adjacent intracochlear electrodes.) In these experiments, we examined the relationship of activation threshold and the width of the response profile measured along the IC tonotopic axis as a function of the proportion of applied current returned via the extracochlear electrode. (The balance of the applied current was returned via two intracochlear electrodes flanking the active electrode.) The results of these studies indicate that intermediate values for threshold and profile width can be obtained, but in no instance did we observe that monopolar response profiles narrowed significantly without a concurrent significant increase in response thresholds. Simple modeling of potential fields supports this observation.

B. Studies characterizing responses to sustained stimulation

1. Single unmodulated acoustic tones

These studies characterized spatial and temporal responses to single unmodulated acoustic tones. This characterization was used as basis for comparison of responses with electrical pulse trains presented on a single channel. They identified a spatial (i.e., stimulus frequency) dependence of temporal responses to pure tones in the inferior colliculus. In particular, neurons with CFs at the stimulus tone frequency typically exhibit a strong onset response followed by a lower-level sustained response that is maintained for the duration of the tone, while neurons with CFs substantially above or below tone frequency typically respond with strong onset which is not followed by a sustained response. These off-CF neurons also frequently exhibited suppression of spontaneous activity following the onset, suggesting lateral or sideband inhibition. The overall result of these frequency-dependent temporal response differences is that the distribution of activity along the IC tonotopic axis is broad at the tone onset and rapidly narrows from both high- and low-frequency directions. The pattern of a broad onset response followed by narrow sustained response cannot be explained by spectral splatter for several reasons: 1) tone onset times used in this study were sufficiently long to ensure that the bandwidths of tone stimuli were narrow, 2) suppression of spontaneous activity was apparent in some cases for IC depths (CFs) above and below the stimulus frequency – an observation not consistent with spectral splatter, and 3) we observed no similar broad responses to the ramped stimulus offset, which was of the same duration as the onset. (Also see discussion of responses to unmodulated electrical pulse trains below.) In some cases, rebound activation was also observed following the offset of the tone stimulus.

2. Studies using single unmodulated electrical pulse trains

In these studies we characterized spatial and temporal responses to single unmodulated electrical pulse trains. In general the responses are consistent with those described above for unmodulated tones. These include 1) narrowing of spatial distribution with time, especially for stimulation with higher (>250 pps) pulse rates, 2) a gradual diminishing of the sustained response even at the most sensitive sites, and 3) a diminishing phase-locked response as the pulse rate increases. For very high rates (>1000pps) there is no phase-locked responses at any recording sites and the response distribution narrows dramatically within 30 ms of response onset.. The significance of this narrowing is that the tonotopic spread of these high rate stimuli can be very narrow -- as narrow as or narrower than those evoked by acoustic tones. Concomitantly, the overall sustained response rate may decrease as pulse rate increases. In contrast, responses evoked by lower rate pulse stimuli (<250 pps) display at least some phase-locked activity to individual pulses and, for very low rates, these responses appear similar to a series of onset responses (i.e., broad spatial profile and high in amplitude). The cutoff frequencies for phase-locking are similar to those previously-reported (100-200Hz). Of particular interest is the broad onset response. This broad onset response is of particular interest, since there are no functional hair cells, and consequently also no contribution of cochlear mechanics to the spread of response. It indicates that some mechanism other than spectral splatter is responsible for the broad onset response seen following both acoustic and electrical stimulation. A preliminary presentation of these results was made at ARO this year (Snyder and Bonham, 2007) and will be made again this summer at the Conference of Implantable Auditory Prostheses (CIAP'07).

3. Studies using two unmodulated acoustic tones in forward masking paradigm

These studies sought to characterize spatial and temporal forward masking responses in the IC to acoustic tones. The results of these experiments could then be used as basis for comparison with forward masking in electrical stimulation. During the course of these experiments we identified unexpected mode of forward masking, and this mode merited extensive further study. There appear to be two distinct modes of forward masking in the IC: one that is consistent with peripheral adaptation and one that is not. This second form of masking, which arises from central mechanisms, can be differentiated predominantly by differences in spatial profile of masking. We described this "central masking" in two presentations of our results (Bonham et al, 2004 and Snyder et al, 2005). It has been described subsequently in the forward masking of responses of AI cortical neurons (Sumner et al, ARO, '07). In peripheral masking the best masking frequency occurs at the CF of the unit suggesting that peripheral neural element was adapting to masking stimulus. In central masking the best masking frequency is observed at the probe frequency, regardless of the unit's CF. One model that supports these observations is that IC neurons receive discrete inputs from peripheral elements with broad range of characteristic frequencies. Since this result was unexpected, we were obliged to repeat this study using tungsten microelectrodes and record responses from single units. The results of this work have been reported in our quarterly progress reports and a manuscript will soon be submitted for publication.

4. Studies using two unmodulated pulse trains, or one pulse train followed by an isolated single pulse, in forward masking paradigm

These studies took two forms: In one, the masking pulse train was varied in level and electrode location while the probe pulse was fixed. In the other, the in masking train was varied and the probe was fixed in level and location. These studies characterized spatial and temporal forward masking responses to unmodulated electrical pulse trains. The results are completely compatible with those described (see above) for acoustic forward masking. As with acoustic stimulation, we observed two types of masking -- one that we could attribute to a peripheral mechanism and one that we could not. In the first case, the best masking electrode was the one to which the recording site was most sensitive, while in the second the best masking electrode was the one on which the probe stimulus was delivered regardless of its sensitivity. Preliminary reports of this work have been presented (Middlebrooks et al, 2004 and Snyder et al, 2005). Using electrical stimulation, we have observed that the adaptation that we attributed to peripheral process seems to dominate – i.e., that masking occurs predominantly at the masker location (frequency for acoustic stimulation), rather than at the probe location (CF). This may suggest that electrical stimulation more strongly activates the peripheral processes than acoustic stimulation (in comparison with central activation).

C. Complex signals

Real-life acoustic signals are complex and vary in time and in their spectral content. Therefore, we wished to study the responses of inferior colliculus neurons to acoustic and electrical signals that vary in their spectral and temporal content.

1. Studies using two unmodulated interleaved pulse trains

Psychophysics studies with cochlear implant users indicate that perception of a signal presented electrically via a cochlear implant to a deafened ear can be modified by the simultaneous presentation of a second signal. To identify physiological correlates of such perceptual modifications, we characterized spatial and temporal responses in the inferior colliculus to two interleaved trains of electrical pulses presented via a cochlear implant.

Two factors in concert determine the difference in response of a neuron within the central auditory system to a pulse train in isolation and to the same pulse train in the presence of a second, interleaved, train: 1) Depending on the spatial distributions of stimulation by each of the two pulse trains, the effective rate of stimulation to peripheral afferents of the central neuron might be doubled by the the interleaved train, and 2) The interleaved train may elicit activity in other peripheral or central neurons that directly or indirectly affect the response of the first neuron by some mechanism (e.g., by lateral inhibition).

To differentiate between these two factors, we characterized spatial and temporal responses in the inferior colliculus to two interleaved trains presented via a single CI channel and via two distinct CI channels. Presentation of the second train via the same channel eliminated differences in spatial distribution of stimulated peripheral afferents, ensuring that differences in response were due to the first factor described above. This established a baseline for comparison of response to stimulation of two distinct channels.

Preliminary results of these studies were publicly presented at two international meetings, CIAP 2005 and ARO 2006, and a manuscript describing the inferior colliculus response to interleaved pulse trains presented on a single CI channel has been submitted for publication to the Journal of Neurophysiology (Bierer & Bonham). Analysis of data describing responses to pulse trains presented via two distinct CI channels is as yet incomplete. A second manuscript describing these observations will be prepared and submitted for publication when this study has been completed.

Briefly, results of the completed study indicate that temporal adaptation is different for different locations along the tonotopic axis – locations that respond most strongly to pulses delivered via one CI channel tend to adapt less than neighboring locations that respond more weakly. This is consistent with our observations of narrowing response profiles during stimulation using unmodulated acoustic tones. We observed that along a recording trajectory perpendicular to the isofrequency lamina in the inferior colliculus, response profiles were similar in width for stimulation at different cochlear locations, suggesting either animal-to-animal or site-to-site variability of response profile width in the inferior colliculus. We also observed a correlation between the ability of neurons at a given site to faithfully respond to individual pulses in the pulse train (i.e., temporal adaptation) and the width of the spatial profile along a recording trajectory including that site and perpendicular to the isofrequency lamina: IC sites included in broad spatial profiles tended to respond well to pulse trains with doubled rate, and conversely, sites that did not respond well to double rate pulse trains tended to be included in narrower spatial profiles.

2. Studies using single (one carrier frequency) SAM tones and single (one intracochlear electrode) SAM pulse trains

We began our studies of complex signals with the simplest of these signals, sinusoidally amplitude modulated (SAM) tones and pulse trains. We parametrically varied these signals by varying them across a range of levels, a range of modulation depths and a range of carrier frequencies (a range of intracochlear electrodes) and for electrical SAM a range of pulse rates. The minimum level was determined according to minimum threshold response and the maximum level was set relative to the maximum response rate and spatial distribution. This range corresponds loosely to difference between threshold level and maximum/comfort level in cochlear implant users. Modulation depth was varied systematically from 100% modulation to as low as 6.125% modulation. Acoustic carrier frequencies were varied from a few kilohertz to 25 kHz. Pulse train carrier rates were varied from 250 pps to 2000 pps. Results for these single SAM tone and single SAM pulse train studies have been presented publicly (ARO'07) and a manuscript is being prepared.

Responses to s<u>ingle modulated acoustic tone (one modulated carrier)</u> were consistent with the studies of responses to unmodulated tones conducted under this contract, as well as those previously-published by others using single-unit recording techniques. Responses to SAM tones were dependent upon carrier frequency, overall stimulus level, modulation depth and modulation rate. Carrier frequency determined the regions of maximum sensitivity, which corresponded to the ICC region with a CF that matched the carrier. Stimulus level determined the extent of spread across the tonotopic organization of the ICC. Modulation depth and modulation frequency determined the amplitude of the response component phase-locked to the modulation frequency. As modulation depth decreased and modulation frequencies increased (above some level), the phase-locked component decreased. The ICC response to SAM tones could be characterized in some cases as intermediate between an onset and a sustained response to unmodulated tones. That is, at appropriate stimulus levels, for sufficiently low modulation rates and sufficiently high modulation depths the response could be characterized as a series of onset responses, one onset response for each modulation cycle. When modulation depth was decreased or modulation rate was increased, the onset-like characteristic of these responses diminished and the overall response took on a character more similar to sustained responses observed during stimulation with unmodulated tones. The observed cutoff frequency for modulation following was consistent with that observed in earlier studies using single-unit tungsten electrodes.

Responses to <u>single modulated pulse trains (modulation of a pulse train delivered via a single intra-cochlear electrical contact)</u> were similar the responses to single SAM tones recorded in this laboratory using tungsten microelectrodes. Carrier rate had little effect on the responses as long as it was at least 6 times the modulation frequency so that under-sampling of the modulation frequency did not occur. The overall results of the studies using SAM pulse trains indicate that the responses evoked can be predicted largely on the basis of the responses evoked by acoustic SAM tones. The region of maximum sensitivity to SAM pulse train depended upon the intracochlear electrode location (carrier frequency) of the stimulus. The amplitude of the phase-locked response decreased with decreasing modulation depth and increasing modulation frequency. These cut-offs for these variables were similar to those determined using acoustic stimulation. One surprising result was that the onset responses of SAM pulse trains were much more pronounced than those observed to acoustic SAM tones. The initial onset response to the first modulation cycle was much larger and much more broadly distributed than the its acoustic counterpart. This observation has important implications for speech coding in APs.

Studies of simultaneous SAM pulse trains, looking at co-modulation and interference between simultaneous but not co-modulated inputs (differing in modulation frequency and/or phase) are ongoing and will be published when completed.

3. Other ongoing studies

As mentioned above, we have archived data for studies examining the responses to unmodulated pulse trains presented on different channels, responses to two sinusoidally amplitude modulated tones presented simultaneously, and responses to two sinusoidally amplitude modulated interleaved pulse trains. We have acquired some data for each of these studies, but more data need to be acquired and analysis needs to be completed.

4. CI processed speech

Design of experiments for the later part of the contract were driven largely by results from early studies. For example, we concluded that more thorough investigations of interactions between simpler stimulus paradigms (e.g., SAM pulse trains) were warranted before undertaking experiments attempting to characterize auditory system responses to cochlear implant processed speech. We have developed the hardware and software to present multichannel implant processor speech and we intend to conduct these studies in the future.

<u>IV. Effects of Anesthesia – Objective 5</u>

A series of ten initial experiments comparing IC responses of awake guinea pigs with guinea pigs anesthetized with either ketamine/xylazine or Isoflurane failed to identify any significant differences between responses in awake and anesthetized animals. In particular, responses to acoustic tone stimuli were similar in both their spatial extent and in temporal pattern. These findings surprised us, as they differed so dramatically from those reported by Ramachandran and colleagues (1999ab, 2000); their studies formed the basis for our proposal's assertion that response measures in unanesthetized animals were essential for interpretation of (see above) AP physiology. Moreover, based on the incidence of non-monotonic rate intensity functions reported by Syka et al. (2000) in Ketamine anesthetized guinea pigs, we expected to see large numbers of type "O" and type "I" response areas in our anesthetized guinea pigs. To our surprise, we rarely saw such responses in either our anesthetized or un-anesthetized animals. In the first year of this contract, we recorded acoustic responses in 10 guinea pigs, which were anesthetized using Isoflurane, implanted with a multichannel recording probe, allowed to recover from anesthesia. Acoustic responses were recorded in these animals both while they were anesthetized and after anesthesia had worn off, and also after subsequent anesthesia using ketamine/xylazine. We seldom observed the type "O" or type "I" response areas seen in most IC neurons of decerebrate cats and we rarely observed non-monotonic rate/level functions using CF tones. Meanwhile, the average Q10 of the excitatory response area of our recordings closely matched the average reported by Syka and colleagues. Therefore, we concluded that either the differences in these single unit response areas were masked by the multi-unit nature of our cluster recordings or that the response differences between anesthetized and unanesthetized guinea pig IC neurons were small and of secondary importance. Given these small differences, the technical difficulties in studying unanesthetized animals, and the administrative overhead required for unanesthetized animal studies, we concentrated our subsequent studies on anesthetized guinea pigs.

V. Public dissemination of research citing full or partial support by this contract:

Our work under this contract has been extensively reported to the auditory and cochlear implant research communities through several channels: 1) presentation of research results at numerous scientific meetings in poster and podium formats, 2) publication of abstracts describing these presentations, and 3) preparation and publication of manuscripts in archival journals. While the period of contract support has ended, public dissemination of the work completed under this contract has not. Contract-derived research will continue to be presented at scientific meetings by staff and scientists, and additional publications describing contract supported work are in preparation for submission to archival journals.

Manuscripts published/submitted

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