"A Cochlear Nucleus Auditory prosthesis based on microstimulation"

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I: **SUMMARY OF WORK COMPLETED DURING THE LAST QUARTER**

Overview of the project

The auditory brainstem implant (ABI), based on an array of electrodes implanted over the human cochlear nucleus, provides a workable auditory prosthesis for patients whose auditory nerve has been destroyed during resection of 8th nerve tumors. We have been developing an auditory implant based on penetrating microelectrodes distributed across the tonotopic gradient of the posteroventral cochlear nucleus which may provide improved pitch discrimination and improved speech perception in patients with little or no auditory nerve survival.

Design of the Human Cochlear Nucleus Array and the Array Inserter Tool (HMRI).

We have slightly modified the hand-held instrument which will be used to insert the array of microelectrodes into the human ventral cochlear nucleus through the restricted aperture of the translabyrinthine surgical approach to the brainstem (See QPR #6). The end of the instrument's barrel is curved into a 50° bend so that the electrodes will be inserted along the tonotopic gradient of the ventral cochlear nucleus. In the original configuration, this segment of the barrel was 15 mm in length. In some intraoperative trials with a dummy instrument, neurosurgeon Dr. William Hitzelberger noted some difficulty in maneuvering the barrel through the restricted opening of the craniectomy. Therefore, the length of the distal segment was reduced to 11 mm while retaining the 50° angle. This modification required that the force transmission wire within the barrel be replaced with a tapered wire having graded stiffness along the distal 20 mm.

In a cat model, we have begun to evaluate arrays sized for the human cochlear nucleus, in which the diameter of the individual iridium microelectrodes has been reduced to 50 µm (from the original diameter of 70 µm). In our studies with chronic intracortical implantation of high-density arrays, we have noted that reducing the diameter of the microelectrodes reduces the severity of the tissue injury. In trials in which the prototype human CN arrays were implanted into the feline spinal cord and cerebral cortex using the hand-held inserter tool, we observed some gliotic scarring near the tips of the longest of the 70 µm electrodes (QPR #6). We have implanted 2 arrays of 50-µm-diameter microelectrodes into a cat's cerebral cortex. The cat will be sacrificed on April 30. We will adopt the more slender electrodes as the new standard only if there is less injury around the tips of the longest pins. It would not be prudent to adopt the more slender electrodes without good evidence that they induce less tissue injury in this application, since the slender electrodes will be slightly more vulnerable to damage when the array is being handled and loaded into the inserter tool prior to its insertion into the patient's brain.

Animal studies with chronically-implanted intranuclear microelectrodes (HMRI)

During the past two quarters, three arrays of 4 electrodes have been implanted into 3 cats. We have completed the series of experiments in which microelectrodes chronically implanted in the feline posteroventral cochlear nucleus are pulsed for 7 hours/day, on up to 20 successive days. The results of these studies have been compiled into a manuscript ("Chronic Microstimulation in the Feline Ventral Cochlear Nucleus: Physiologic and Histologic effects") which has been submitted to Hearing Research Journal. We also have completed 3 experiments in which we addressed two issues related to the depression of neuronal excitability which develops during prolonged stimulation. First, we investigated whether it is practical to compensate for stimulation-induced depression of neuronal excitability by shifting (remapping) the range of stimulus amplitudes. Also, we investigated whether it is possible to compensate for a neuronal response that is initially elevated as a result of the tip of the stimulating electrode being slightly dorsal or ventral to the cochlear nucleus. The results of these two experiments are described in detail in Section II of this report.

Pitch as a function of pulse rate in the Auditory Brainstem Implant (HEI)

These studies investigated pitch perception in patients who have received the present version of auditory brainstem implant, in which an array of electrodes is implanted on the surface of the brainstem over the ventral cochlear nucleus. These studies were conducted in order to estimate how best to adjust the pulsing rate for the patients that will receive the arrays of penetrating microelectrodes. These studies are described in detail in Section III of this report.

II: The effect of transposition of the stimulus amplitude to compensate for stimulation effects and ectopic electrode placement (HMRI)

These studies were conducted as part of our program to develop protocols for safe and effective microstimulation in the human cochlear nucleus.

Microstimulation permits excitation of a localized population of neurons, and thereby allows access to features of neuronal organization that are not accessible with larger (macro) electrodes. However, the localization of the stimulus current to the immediate vicinity of the microelectrode also means that the neurons close to the microelectrodes are excited repeatedly. In contrast, with normal sensory inputs, or when stimulating with macroelectrodes, the neuronal activity would be distributed over a much larger population. One consequence of this persistent, focused stressor is a long-acting depression of neuronal excitability. We investigated whether it is practical to compensate for the depression by transposing the range of the stimulus. We also investigated a related problem; the situation in which a neuronal threshold is elevated not as a result of electrical stimulation, but because the microelectrode is slightly out of position.

METHODS

Iridium stimulating microelectrodes are fabricated from lengths of pure iridium wire, 70 µm in diameter. The entire shaft and wire junction is coated with 3 thin layers of Epoxylite 6001-50 heat-cured electrode varnish. The insulation is removed from the tip with an erbium laser, leaving an exposed geometric surface area of 2000 +/- 400 μm^2. The individual electrodes are assembled into an integrated array of 4 microelectrodes spaced approximately 400 µm apart. The iridium electrodes are "activated" to increase their charge capacities. They are cleaned, soaked in deionized water for 24 hours, and sterilized with ethylene oxide.

Young adult cats are anesthetized with Pentothal sodium, with transition to a mixture of nitrous oxide and Halothane. A pair of stainless steel recording electrodes is implanted by stereotaxis into the right inferior colliculus through a small craniectomy. A small craniectomy is made over the cerebellum, through which the array of iridium stimulating electrodes is implanted into the left posteroventral cochlear nucleus (PVCN).

The regimen of prolonged stimulation was implemented 50 to 500 days after implantation of the electrodes (54 to 135 days, for the cats described in this report). For the prolonged stimulation regimen, we have simulated an acoustic environment based on a computer-generated artificial voice that was specified and provided by the International

Telegraphic & Telephony Consultive Convention, for the purpose of testing telecommunication equipment (CCITT, 1988). The CCITT artificial voice reproduces many of the characteristics of real speech, including the long-term average spectrum, the short-term spectrum, the instantaneous amplitude distribution, the voiced and unvoiced structure of speech, and the syllabic envelope. The artificial voice signal was passed through a full wave rectifier and then underwent logarithmic amplitude compression, before being sent through an appropriate anti-aliasing filter. The amplitude of the signal from the filter then sets the amplitude of the charge-balanced stimulus pulses, which were delivered to each electrode at 250 Hz per electrode, in an interleaved manner. The range of pulse amplitudes was shifted so that acoustic silence is represented by a pulse amplitude that is close to the threshold of the response recorded in the central nucleus of the inferior colliculus while stimulating in the PVCN. Typically, the response threshold is 6 +/-1 μA when the stimulus pulse duration is 150 μs per phase, and 14 +/- 2 μA when the duration is 40 μs/phase.

The artificial voice signal was presented for 15 seconds, followed by 15 seconds in which the stimulus amplitude was held near the threshold of the evoked response (6 or 14 μA, as noted above). This 50% duty cycle is intended to simulate a moderately noisy acoustic environment. The stimulation and data acquisition was conducted using a two-way radiotelemetry stimulation and data acquisition system, and the cats are able to move about freely in a large Lucite cage.

Before and after each daily session of stimulation, 1024 to 4096 responses evoked from each of the microelectrodes in the PVCN were recorded in the inferior colliculus, and these were summated (averaged) to obtain averaged evoked responses (AERs). The amplitude of the first and second components of the AER was measured from the peak of the positivity to the trough of the subsequent negativity (Figure II-1). Because of its short (~ 1 ms) latency after the stimulus, the 1st component of the AERis assumed to represent neuronal activity evoked directly in the neurons projecting from the PVCN to the inferior colliculus, while the second component may represent neuronal activity that is evoked transsynaptically. All of the response growth functions described in this report were generated from the first component.

The response growth functions (RGFs), which represent the recruitment of the neural elements surrounding the microelectrode, were generated for each stimulating microelectrode,the amplitude of the first component of the AERs evoked from the microelectrode is plotted against the amplitude of the “probe” stimulus that evoked the AER. The RGFs were generated before, and also immediately after the 7-hour sessions

of stimulation. The frequency of the "probe" stimulus was 50 Hz, which is much lower than that of the 250 Hz used during the 7-hour stimulation session. Since these RGFs were not acquired during the 7-hour session, and not contemporaneously with the LCAVS-modulated stimulus, we refer to them as "non-embedded response growth functions". In addition, a limited number of "embedded" RGFs were acquired during the first and last hour of some of the 7- hour sessions of stimulation with the artificial voice signal, at the full stimulation rate of 250 Hz per electrode. The procedure for generating the embedded RGF's is described in detail in Quarterly progress report #5 (Contract No. NO1-DC-5-2105).

The non-embedded RGFs reveal depression of neuronal excitability that persists after the end of the 7 hours of high-rate stimulation with the artificial voice signal. This type of persisting stimulation-induced depression of neuronal excitability, which we have dubbed "SIDNE", may persist for many days (McCreery et al, 1997) . The occurrence of marked SIDNE may identify stimulation protocols that place significant stress on the neurons of the ventral cochlear nucleus. The embedded RGFs reveals how the regimen of prolonged stimulation affects these neuron's responses to the actual artificial voice signal, and also reveals short-acting neuronal refractivity during the high-rate pulsing which is not detectable in the non-embedded responses that are acquired at a much lower pulsing rate. The non-embedded and embedded responses, and the histologic evaluation of the implant sites, together provide a more complete picture of the safety and efficacy of the stimulation regimen.

Within 15 minutes after the end of the last day of stimulation, the cats were deeply anesthetized with pentobarbital and sacrificed for histologic evaluation of the electrodes sites.

RESULTS

Figure II-2 shows the nonembedded and embedded response growth functions of the first component of the evoked response recorded in the inferior colliculus during the first 3 days of a 20-day stimulus regimen (cat CN137) in which the electrodes were pulsed for 7 hour per day. The logarithmically-compressed artificial voice signal (LCAVS) modulated the amplitude of the 150 μs stimulus pulses over the range of 6 and 20 μA, with 6 μA corresponding to acoustic silence. By the end of the first day (7 hours) of stimulation, the left (low amplitude) end of the range of the non-embedded RGF had become shifted downwards and to the right. This is a manifestation of stimulation-induced depression of neuronal excitability (SIDNE) which may persist for many days (McCreery et al., 1997). Just prior to the end of the 7 hours of stimulation with the LCAVS, the embedded RGF was acquired. The embedded RGF is shifted to the right of the nonembedded RGF that was acquired immediately after the 7-hour session (and using the low- frequency probe stimulus). The separation between the embedded RGF and the subsequent nonembedded RGF represents short-acting neuronal refractivity. ("Short-acting" because it is not apparent in the subsequent nonembedded function.)

There are two consequences of the changes that occur during the prolonged stimulation; a reduction of the dynamic range of the neuronal response and the appearance of a partial "dead band" at the lower end of the neural response range. Both phenomena may affect the performance of a patient using an auditory prosthesis based on intranuclear microstimulation.

The change in the embedded RGF during prolonged stimulation probably conveys the best indication of how the prolonged stimulation will affect a patient's auditory perceptions across the range of stimulus amplitudes. The data plotted in in Figure II-3 are from an experiment in which three intranuclear microelectrodes were pulsed for 7 hours per day on each of 6 sucessive days (cat CN138). The LCAVS modulated the 150 μs stimulus pulses between 6-20 μA, and the pulse rate was 250 Hz per electrode. At the beginning of the 1st day of the 6-day regimen, the embedded RGF spanned essentially the entire range of stimulus amplitudes, but by the end of the first day (7 hours), the lower (left) portion of the RGF had shifted so as to reduce the dynamic range of the embedded RGF and also had created a partial "dead band" in the lower part of the stimulus range. This state of affairs remained essentially unchanged throughout the third day of stimulation. On the 4th day, the stimulus range was transposed upwards so that acoustic silence now was represented by a pulse amplitude of 11 μA and the maximum pulse

amplitude was 25 μA. During the 4th day (the first day with the transposed range of stimulus amplitudes), the embedded RGF became shifted farther to the right, and by the end of the 6th day, the dynamic range of the neural response was actually slightly less than was the case before the stimulus range was transposed. Figure II-4 shows a similar result from another cat (CN139). In both of these animals, transposing the stimulus range did not restore the dynamic range of the nonembedded response growth function. However, in cat CN138 (Figure II-3), the transposition does appear to have reduced the width of the dead band.

If the electrical threshold is initially elevated, it may be feasible to compensate by transposing the range of the stimulus amplitudes. Figure II-5 shows the embedded RGF's from an electrode in cat cn138 that had actually penetrated through the ventral surface of the cochlear nucleus (by approximately 200 μm), and consequently, the threshold of the nonembedded response was nearly 30 μA (rather than the typical value of 6 μA when the stimulus pulse duration is 150 μs). This ectopic electrode placement would be analogous to the situation in which an electrode in a clinical device had passed through the human cochlear nucleus and into the inferior cerebellar peduncle. The electrode was pulsed for 7 hours/day on 10 successive days, at 250 Hz, and the 150 μs stimulus pulses were modulated between 30-50 μA by the LCAVS. This stimulus produce SIDNE by the end of the first 7 hour session, but the nonembedded and embedded RGFs subsequently were very stable throughout the remainder of the 10-day regimen and the embedded RGF spanned nearly the entire range of the stimulus pulse amplitudes. In this animal, the stimulus charge per phase reached 7.5 nC, but the neurons and neuropil in the cochlear nucleus dorsal to the tip site were undamaged. We have previously shown that 7 hours of continuous pulsing at 500 Hz and with a charge per phase greater than 3 nC/ph will induce micro-vacuolations in the myelinated axons adjacent to the intranuclear microelectrodes (McCreery et al., 1994). This did not occur in this animal, probably because the stimulus pulse rate was lower (250 Hz), and also because only a portion of the stimulus pulses reached the maximum amplitude and because the electrode tip was slightly outside of the nucleus, and therefore, was not surrounded by myelinated axons.

DISCUSSION

The combined effect of SIDNE (as revealed in the shift of the non-embedded RGF) and of the short-acting neuronal refractivity (as revealed in the separation between the embedded RGF and the supsequent non-embedded RGF) is to depress the neuronal response near the response threshold, and therefore, to reduce the total dynamic range

of the neuronal response. These phenomena may have the greatest effect on the performance of a clinical device at the low end of the range of stimulus amplitudes where a partial dead band may develop. If a dead band does develop in a clinical device, and if this causes degradation of a patient's performance, then it may be possible to transpose the entire range of stimulus amplitudes upwards by a few μA and at least partially out of the dead band. However, the data presented in this report suggests that this strategy may be of limited value since increasing the stimulus amplitude will exacerbate the SIDNE.

Figure II-5 illustrates that it is possible to compensate for an initially high neuronal response threshold (in this case, due to the stimulating electrode being slightly out of position) by shifting the entire range of stimulus amplitude so that acoustic silence corresponds to the elevated response threshold (or in the case of a clinical device, to the patient's perceptual threshold). In a clinical prosthesis, this strategy should be reserved for instances in which threshold of the electrically-evoked auditory percepts are elevated, since prolonged stimulation at a high charge-per-phase carries a risk of injury to myelinated axons that pass within 100 μm of the electrode tip (McCreery et al., 1994). In a human patient, an electrode tip that penetrates completely through the cochlear nucleus would reside in the inferior cerebellar peduncle, and the consequences of damaging the axons that pass very close to the electrode is uncertain.

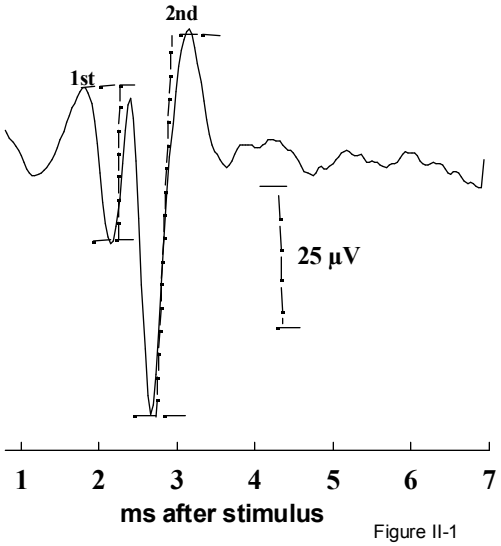

Figure II-1

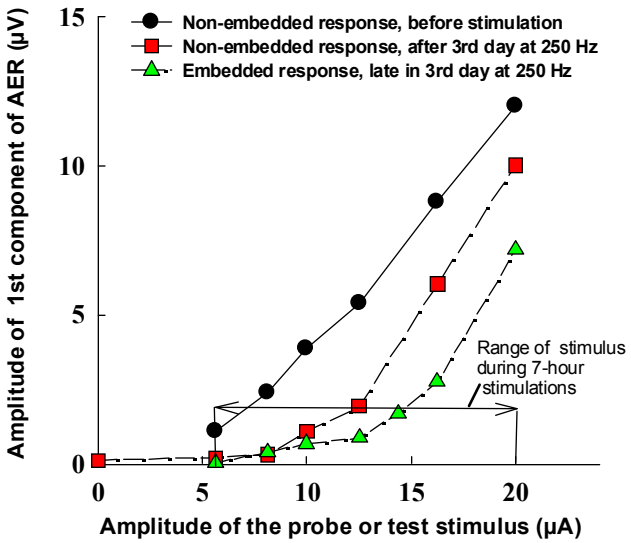

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Figure II-2

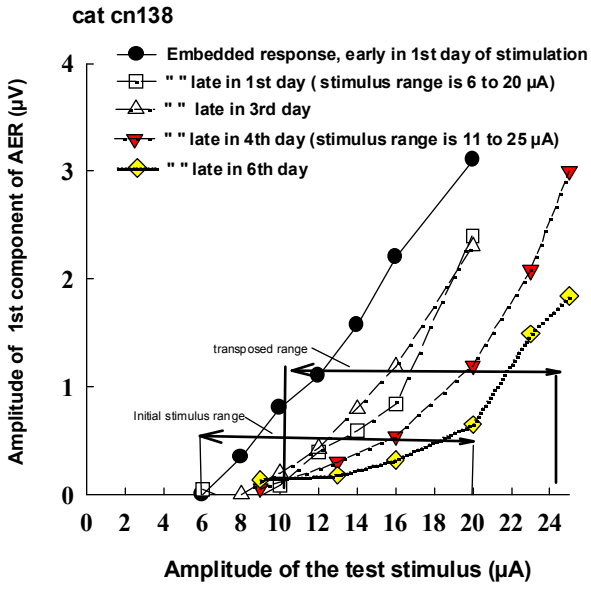

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Figure II-3

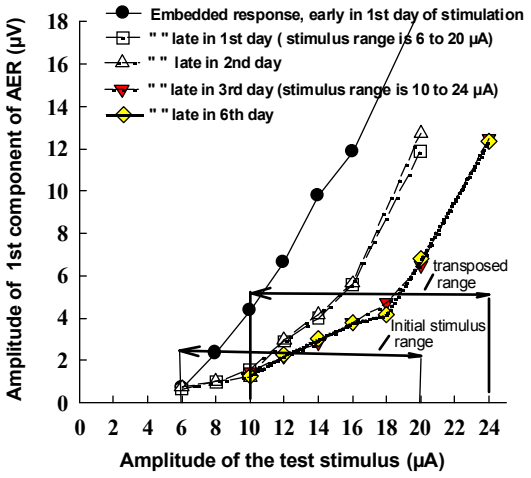

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Figure II-4

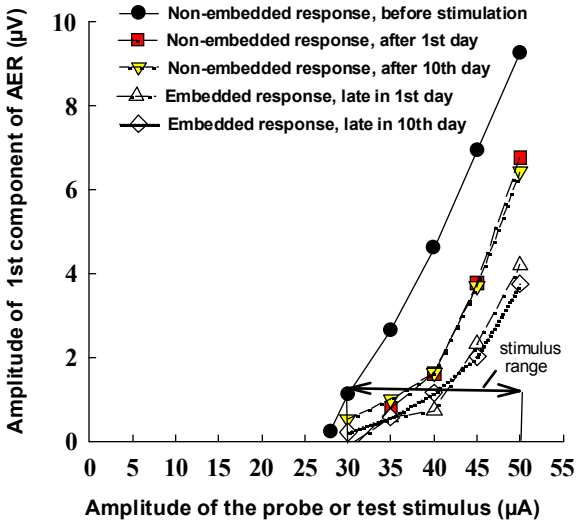

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Figure II-5

III- Pitch as a function of pulse rate in the Auditory Brainstem Implant (HEI)

INTRODUCTION

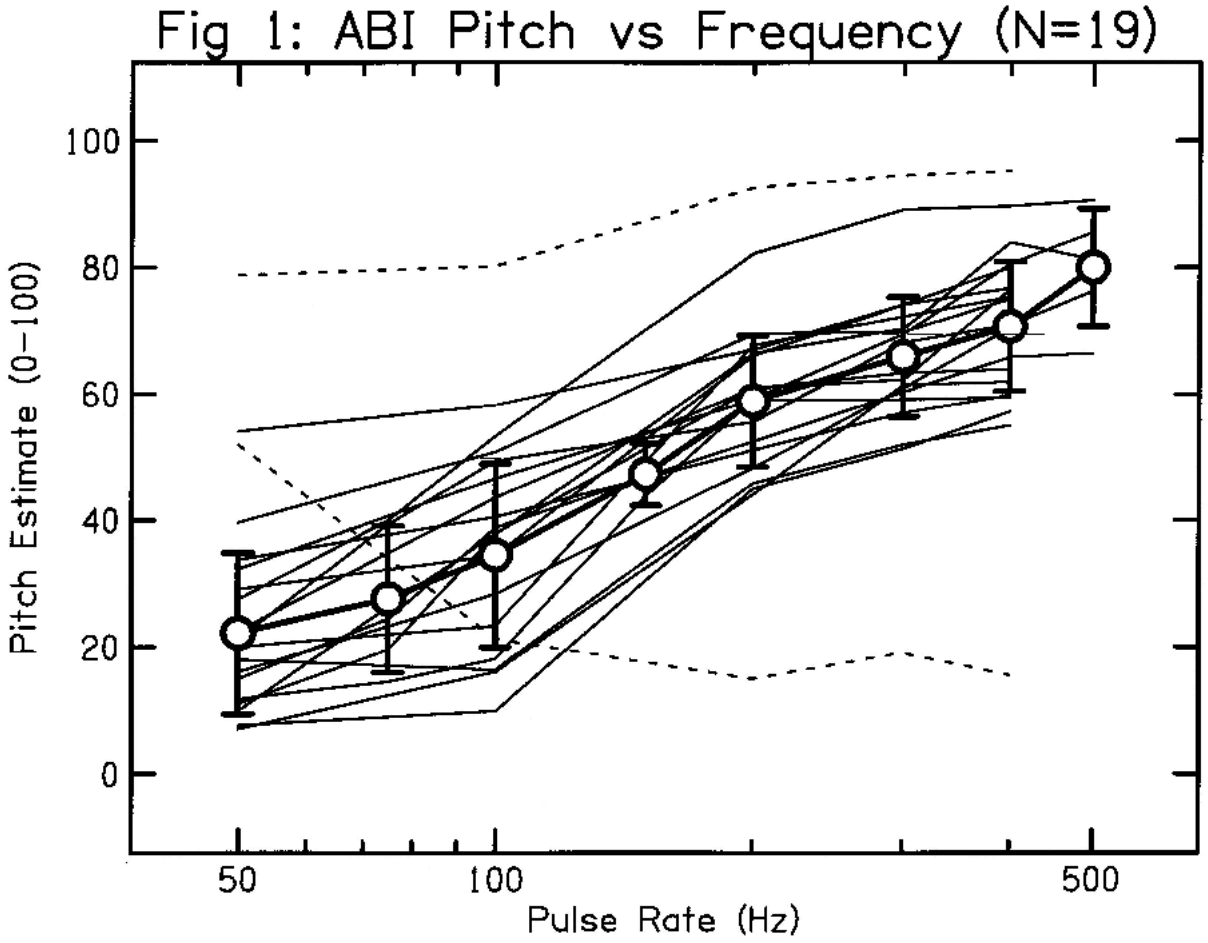
The success of multichannel cochlear implants is due to the ability of each electrode to stimulate a separate population of neurons in the cochlea that elicits a distinct pitch. There is some indication that patients who have less pitch differences between their electrodes do more poorly at speech recognition. In the existing clinical auditory brainstem implant (ABI) most patients perceive little difference in pitch across their electrode array, which may be the factor that limits speech recognition performance with the ABI. The small difference in pitch between surface ABI electrodes is likely due to the fact that the tonotopic dimension of the human cochlear nucleus is orthogonal the axis of the surface electrode array. The present contract is intended to overcome this problem by developing arrays of penetrating microelectrodes so as to achieve intimate connection to different tonotopic layers of the cochlear nucleus.

With penetrating microelectrodes, the neurons of the cochlear nucleus are in close proximity to the stimulating electrode, and frequency-specific stimulation can be achieved (McCreery et al, 1998). Animal experiments have shown (McCreery et al., 1997) that repetitive high-rate stimulation with penetrating microelectrodes in the cochlear nucleus can cause stimulation-induced depression of neural excitability (SIDNE). McCreery et al. observed that the threshold and growth of evoked response curves shift to higher stimulation levels after only a brief exposure to stimulation at rates above 100 Hz. In some cases this SIDNE persisted for days or even weeks following stimulation. Thus, SIDNE could present a problem for a prosthesis based on intranuclear microstimulation because the level of stimulation would need to be continuously increased to maintain the same perceptual level, and for this reason, we have used a pulsing rate of 250 Hz in the long-term animal studies conducted at HMRI. (and see Section II of this report).

In cochlear implants the current trend is to use stimulation pulse rates that are as high as possible. Higher pulse rates allow the representation of higher frequencies of temporal information, and very high pulse rates may cause the nerve to fire in a more stochastic mode rather than the highly deterministic mode observed at lower stimulation rates. SIDNE-type adaptation effects have not been observed with electrical stimulation of the primary auditory nerve with a cochlear implant. High stimulation rates may be useful in ABI signal processing as well, but the existence of SIDNE may offset any benefit of high stimulation rates.

The present study was undertaken to document the change in pitch associated with stimulation at the surface of the human ventral cochlear nucleus, at different pulse rates. In cochlear implants the pitch of the electrical stimulation depends on which electrode is pulsed and on the rate of stimulation. In general, pitch increases with stimulation pulse rate up to about 300 Hz. At 300 Hz and above, the pitch is determined by the tonotopic location of the electrode. A few cochlear implant patients report an increase in pitch as pulse rate was increased up to 800 Hz or higher. For the auditory brainstem implant only a small amount of data is available on the change in pitch with stimulation pulse rate. That preliminary data showed that pitch did not increase for pulse rates above 150 Hz - a much lower pitch saturation frequency than for cochlear implant listeners.

In normal acoustic hearing, listeners are able to hear temporal modulations and receive a temporal pitch sensation for modulations up to 300-500 Hz (Viemeister, 1979, Burns and Viemeister, 1981). When only temporal cues are available it appears that the auditory system is limited to information below 300-500 Hz. A similar limit appears to hold for cochlear implant listeners (Shannon, 1983, 1992), although there may be exceptional patients who can use temporal information up to much higher rates. The present experiment measured pitch as a function of pulse rate in 19 patients with the surface electrode ABI.



METHODS

Nineteen subjects participated in this experiment. All subjects had auditory brainstem implants with eight-electrode surface arrays (Otto et al., 1998). An electrode pair was chosen for stimulation that had relatively low thresholds and a medium pitch percept.

Stimuli with rates of 50 to 500 Hz were adjusted for equal loudness. Pulse duration was typically 200 or 400 us/phase. The stimulus pulses were delivered in bursts that were 250 ms in duration. Stimulus order was randomized with respect to frequency and the stimuli presented to the subjects one at a time. After each stimulus the subject was instructed to assign a number from 1 to 100 corresponding to the pitch of the stimulus.

They were instructed to use the scale of 1-100 to represent the entire pitch range, i.e., to use small numbers to represent the lowest pitches they could imagine (fog horns, deep bass notes, etc) and to use high numbers to represent the highest pitches they could imagine (cymbals, high-whistles, fingernails on the blackboard, etc). In some cases a few subjects were presented with randomly selected pairs of stimuli and were asked to assign a number for the pitch of each sound. At least 10 pitch judgements were collected for each stimulus.

RESULTS

Figure III-1 presents the pitch estimates as a function of pulse rate for nineteen ABI patients. The open symbols with error bars represent the average pitch estimates from 17 of the 19 subjects. The two subjects whose data are plotted with dashed lines had significantly different patterns of pitch perception than the other subjects and so were not included in the average. One subject showed relatively little change in pitch across the range of stimulus frequencies; all stimulus rates were heard as quite high in pitch. The other subject showed a decrease in pitch with increasing rate - a trend opposite that of all other subjects.

For most subjects, pitch increased with pulse rate throughout the frequency range from 50-500 Hz. For some subjects there is some indication that pitch saturates at a frequency of 300 Hz, similar to what has been observed in patients with cochlear implants, but many subjects show a clear increase in pitch perception from 300 to 500 Hz.

DISCUSSION

At present, ABI patients have relatively poor speech recognition. Although most patients have 6-8 functioning electrodes, their speech recognition performance is equivalent to that of normal-hearing listeners with noise-band speech processors using 1 or 2 channels (Otto et al., 1998). When such limited spectral cues are available, patients are forced to rely more heavily on temporal cues. The pitch data presented in this report suggest that ABI patients are capable of perceiving pitch changes as a function of stimulation rate as capably as are normal-hearing listeners or cochlear implant listeners. If ABI users are limited to single-channel stimulation, they will benefit from temporal cues up to 500 Hz. However, recent results have shown that when even two spectral channels of spectral information are available, listeners don't appear to use temporal information above 20 Hz (Fu et al., 2000). This may be important for ABI patients with penetrating electrodes, because with the penetrating microelectrodes high stimulation rates may cause

SIDNE. If penetrating electrode systems can produce distinct pitch sensations from different electrodes and thus convey multiple channels of spectral information, the stimulation rate may not have to be too high. One possible negative aspect of low pulse rate stimulation is that the carrier pulse rate will produce its own distinctive pitch. Even if high pulse rates are not required for conveying speech information, the pitch produced by a low pulse rate may interfere with speech recognition. In patients with cochlear implants it has frequently been observed that low pulse rates produce a buzz-like percept that can interfere with speech recognition. Thus, although very high pulse rates are not necessary for representing rapid temporal changes in speech, the carrier rate should be sufficiently high so that it does not produce a pitch percept of its own. The present data suggest that the pulse rates must be higher than 500 Hz. As noted in Section II of this report, the strategy of remapping the range of amplitudes spanned by the stimulus pulses in order to compensate for the stimulation- induced depression of neuronal excitability, may have limited utility. However, since logarithmic compression of the speech signal causes most of the stimulus pulses to be clustered in the upper part of the range of stimulus amplitudes, the loss of neuronal response at the lower end of the range may not greatly affect the patient's performance. If high pulse rates produce SIDNE in patients with ABI devices using penetrating microelectrodes, and if the SIDNE appears to degrade their ability to perceive speech, then it will be necessary to investigate the trade-off between SIDNE and the interfering pitch percepts, as a function of the carrier rate.

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