Comparisons of psychophysical and neurophysiological studies of cochlear implants

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This paper compares psychophysical and neural studies of electrical stimulation of the auditory nerve with the goal of evaluating the relevance of single-unit animal models for the development of cochlear prostheses for profoundly deaf humans. Comparative psychophysical studies with implanted deaf subjects indicate that animal models, at least nonhuman primates, provide a close match to humans, though this is not always true for acoustic stimulation of normal-hearing subjects. However, the human-animal comparisons, especially those involving electrical stimuli, need further study using more carefully matched conditions. Comparisons of psychophysical and neurophysiological thresholds for electrical stimulation in animals reveal consistently higher thresholds in the neural studies. A number of factors which may account for these differences are discussed. A partial resolution of the problem could result from conducting neurophysiological and behavioral studies in the same animal. Finally, comparison of psychophysical and neurophysiological studies of temporal encoding suggest that there may be more information encoded in the auditory nerve than is used by the system, at least for non-spectral frequency discrimination. This points to a need for further analysis of the processing of this information at higher levels in the auditory pathway.

Introduction

One of the newest applications of the single-unit animal model, and one of the most exciting in terms of its potential benefit to clinical otolaryngology, involves the neurophysiological study of cochlear implants. At least five laboratories around the world are actively engaged in single-unit studies involving electrical stimulation of the auditory nerve. It seems appropriate therefore to evaluate this animal model using some of the approaches discussed in this workshop. I will begin with the comparative psychophysics approach.

Comparative psychophysics

For acoustic stimuli, the nonhuman mammals typically used for single-unit recording are roughly equal to or better than humans in detecting stimuli, particularly at high frequencies, but are typically worse than humans in discriminating frequency or intensity changes (Fay, 1988). For electrical stimulation the picture is quite different. The evidence to date (detailed below) indicates little or no difference in performance between humans and animals on any of these tasks. Note that conclusions at this time must be limited to human versus nonhuman primates, as data on the psychophysics of electrical stimulation for other nonhuman mammals is sparse. Given the neuroanatomic data on species differences in the auditory nerve and CNS auditory pathways (Nadol, 1988; Moore, 1987), it should not be assumed that the monkey data will apply to other mammals. Additional psychophysical studies are needed in other species, particularly cats and guinea pigs which are commonly used for single-unit studies.

Comparison of psychophysics across animals which differ anatomically may lead to insights as to the functional role of the anatomical structures. Particularly intriguing is the presence of reciprocal synapses on outer hair cells which seem to occur normally only in higher primates (Nadol, 1988).
As Fay (1988) pointed out, comparison of hearing across species, which in many cases means comparison across laboratories, is fraught with difficulties. Nevertheless, there is sufficient consistency across a number of studies to be convincing, at least with regard to the acoustic signals discussed by Fay. With cochlear implants the problems are worse because the numbers are smaller, and because in many cases sufficient details of the experimental procedures do not appear in the literature. Nevertheless, the findings to date point to similarities between human and nonhuman performance more strongly than they point to differences. I will review those data briefly below.

Thresholds for electrical stimulation of human and nonhuman-primate subjects are compared in Fig. 1 and 2. The six nonhuman primate cases were chosen to represent a range of nerve survival patterns comparable to that seen in humans by Hinojosa and Marion (1983) and represents the full range of thresholds we have seen in 30 cases where nonhuman primates with scala tympani implants in deaf ears were tested psychophysically. Thresholds for human subjects obtained by other investigators (Fig. 2) show similar shapes and cover a similar range of currents. One difference between these two sets of data is the higher slopes of some human threshold contours between about 60 Hz and 200 Hz. This deserves further study.

Dynamic ranges for electrical stimuli also assume similar values in human and nonhuman primates. In both species, dynamic ranges are larger at low frequencies (around 100 Hz) than at high frequencies (above 500 Hz) (see review by Pfingst, 1984). Data at this time are insufficient to allow more detailed comparisons.

Level difference limens for electrical stimuli, obtained from monkeys, show a clear dependence on the frequency and level of stimulation (Pfingst et al., 1985)}
Fig. 2. Threshold contours for six human cases. Thresholds for monopolar sinusoidal stimulation of electrodes in the basal turn of the scala tympani are shown. The subjects' initials, electrode designations, and sources of the data are shown in the inset.

earlier published reports on implanted humans stated that electrical level difference limens were constant across frequency and level, suggesting a significant species difference. However, more recent data by Shannon (1983) (Fig. 4) show the same relationships as those seen in the data from monkeys. Furthermore, the ranges of level difference limens for the two species largely overlap.

Frequency difference limens for electrical stimuli for humans and monkeys also overlap. Fig. 5 compares human data from the literature (open symbols) and monkey data from our laboratory (filled circles). A wide range of values for human subjects are found in the literature but the data for nonhuman primate fall in the middle of this range. These comparisons are complicated by several factors. There is ambiguity regarding the level at which some of the human data were collected. Clearly, stimulus level significantly affects the magnitude of frequency difference limens, as illustrated in Fig. 5 by the data for the monkey at three levels at 100 Hz. Furthermore, there is uncertainty about whether the human subjects were using loudness cues. In studies in monkeys we have found that deviations in level

* It is possible that these earlier statements regarding electrical intensity difference limens were based on too little or too variable data. It is also possible that for selected stimulus parameters level difference limens are constant across level (White, 1984). This later possibility deserves further study.
from the equal-loudness point by only a few tenths of a dB are sufficient to significantly increase the percent hits in a frequency-level discrimination task (Pfingst and Rush, 1987). We suspect that in most frequency discrimination experiments with implanted human subjects loudness has not been matched to a degree sufficient to completely eliminate loudness cues, which therefore suggests that some of the human frequency difference limens reported in the literature are artificially low. This reinforces our view that monkeys do at least as well as humans in discriminating changes in the frequencies of electrical sinusoids.

Fig. 6 summarizes data from a number of studies on the discrimination of electrical and acoustic frequency changes by humans and monkeys. Ranges of values obtained across subjects by various laboratories are shown. For the acoustic data, perhaps the best comparison between the monkeys and humans for our purposes would use the data from Spiegel and Watson for non-musicians (range c). These subjects received little training in the task and thus would be expected to perform no better, on the basis of training, than cochlear implant subjects. Even under these less than ideal conditions humans perform better than well-trained monkeys in the majority of cases. The data for the monkeys (range d) overlap only the upper 20% of the range of the human data (on a log scale) and extend beyond this range. In contrast, when the performance of a subset of these same

Fig. 4. Level difference limens for a human subject at two different frequencies of sinusoidal stimulation, plotted as a function of initial stimulus level. Dynamic range was 30dB at 100 Hz and 18dB at 1 kHz. (From Shannon, 1983)
monkeys on an electrical frequency-discrimination task (range f) is compared with data from the literature on electrical frequency discrimination in humans (range e), the monkey data fall approximately in the middle of the range of values reported for the humans. Interestingly, this range is also close to that reported for humans using acoustic signals which lack spectral cues for the frequency change (range g).

Obviously, when comparisons of this sort are made using data from different laboratories collected under different conditions there is a risk that the results are due to differences in procedure rather than species. However, some of these comparisons have been made in the same laboratory using the same equipment and procedures. Under these conditions, Sinnott et al. (1985) found that monkeys had higher pure tone frequency difference limens than humans. Long and Clark (1984) studied difference limens for the frequencies of pure tones and SAM noise in chinchillas and humans and concluded that the human-animal differences are much smaller for nonspectral frequency discrimination than for frequency-discrimination involving spectral cues. Clearly we need additional work in the area of electrical frequency discrimination. The studies should be conducted using human and monkey subjects which are closely matched with regard to stimulus parameters, implant type, thresholds, dynamic ranges, and degree of training. Procedures and equipment should be matched as closely as possible. However, if forced to make a choice at this point I would say that the evidence is in favor of little or no difference between human and monkey performance on these tasks for electrical stimulation.

These comparisons are rather important for interpreting the neurophysiological data from both normal-hearing animals and deafened, electrically stimulated animals. They suggest the interesting hypothesis that the monkey-human differences observed with acoustic stimulation may relate to differences in the spectral analysis or in the central processing of place information. They also suggest that the responses of these two species to temporal information may be similar. If this conclusion is correct then we are justified in using psychophysical data from either humans or monkeys to interpret the single-unit data obtained on temporal encoding of frequency information.

**Comparison of neurophysiology to psychophysics**

**Thresholds**

I turn now to a consideration of neurophysiological studies which have been done with cochlear implants, and the relation of these to the psychophysical data. Again, I will begin with a consideration of thresholds. Fig. 7 compares behavioral thresholds for six monkeys with varying degrees of nerve survival, as in Fig. 1, with ranges of thresholds of auditory nerve fibers or anteroventral cochlear nucleus units from published data from five different laboratories. The neural thresholds are plotted as a function of the stimulus frequency for sinusoidal stimulation or the inverse of the pulse period for pulsatile stimula-
Fig. 7. Contours $a-j$ are psychophysical threshold contours for six monkeys from Fig. 1. The range bars indicate the ranges of thresholds reported for auditory nerve fibers and cochlear nucleus neurons from cats and guinea pigs as described below. $g =$ Glass, 1983: AVCN, anesthetized guinea pigs, scala tympani electrodes with 1 mm separation, sinusoïds, the cochlea was not treated with neomycin, 88 units, mode = 28 $\mu$Amp rms. $h =$ Hartmann et al., 1984: auditory nerve, anesthetized cats, round window monopolar stimulation. $hss =$ sinusoïds, 'intact' cochleas, synchronization thresholds, mean = 26.3 $\mu$Amp rms. $hfr =$ sinusoïds, 'intact' cochleas, rate thresholds, mean = 40.1 $\mu$Amp rms. $hp =$ 0.2 msec/phase pulses, mechanically and chemically destroyed cochleas. $j =$ Javel et al., 1987: auditory nerve, anesthetized cats, Scala tympani electrodes with 0.75 mm separation, pulses, no neomycin. $k =$ Kiang and Moxon, 1972: auditory nerve, anesthetized cat systemically treated with neomycin, round window to apex electrodes, sinusoïds, 22 fibers. $v =$ van den Honert and Stypulkowski, 1984: auditory nerve, anesthetized cats, Scala tympani electrodes with 2 mm separation, pulses, 16 fibers, mean = 104 $\mu$Amp.

tion. This representation for pulses is based on observations that pulse width is the major determinant of psychophysical threshold with pulse rate playing a minor role under most circumstances (Eddington et al., 1978; Pfingst et al., 1979, 1980; Shannon, 1985). At pulse rates sufficient to produce a square wave, psychophysical thresholds for rectangular pulses are equivalent to those for sinusoïds of equal period (Pfingst et al., 1980; Shannon, 1985). Represented in this way, the neural thresholds are consistently higher than the behavioral thresholds for comparable parameters.

A number of factors may be hypothesized to account for these differences, and given the large number of differences between the electrophysiological and behavioral experiments, the reasons for these differences cannot be resolved at this time. Possible contributors to the differences are single unit sampling bias, definitions of thresholds (Rose et al., 1971; Geisler et al., 1985), differences in electrode design and placement, differences in the waveforms used, and species differences. Physiological alteration of the preparation as required for single-unit studies as well as trauma due to the implant and/or procedures used to destroy hair cells must also be considered. In behavioral studies we have sometimes seen marked elevations in behavioral thresholds within the first few days after the implant surgery relative to the lower stable thresholds achieved several weeks after surgery (Pfingst et al., 1979). We hypothesize that these effects are due to temporary trauma from the implant and/or the deafening procedures. Clopton and Glass (1984) found that thresholds of ventral cochlear nucleus neurons were elevated in
guinea pigs with neomycin treated co&leas as compared with those from animals with untreated cochleas.

The significance of these discrepancies between behavioral and neural thresholds depends on their cause. If they are due to species differences, differences in stimulation procedures, or differences in physiological treatment of the cochlea or the animal, these are matters which may simply help us better understand the important variables affecting electrical stimulation. On the other hand, if they are due to sampling bias or threshold definition, we must be concerned that the levels used in the physiological experiments may not be in a range appropriate for comparison with behavioral studies.

The basis of the discrepancies between behavioral and neural thresholds might be partially resolved by making the psychophysical measurements and the neural measurements in the same animal at the same time using chronic single-unit recording techniques. This approach would eliminate all of the hypothesized causes of these differences except sampling bias and threshold definition.

Other interesting and potentially very useful comparisons can be made between behavioral and neural thresholds for electrical stimuli, though their interpretation depends to some extent on knowing the relationships of the actual levels used in each case. For example, the tuning curves for auditory nerve fibers (Kiang and Moxon, 1972) and anteroventral cochlear nucleus neurons (Glass, 1983) for sinusoidal electrical stimuli show some similarities to the behavioral threshold contours for these same stimuli. In both neural and psychophysical data, the maximum sensitivity (lowest threshold currents) is in the region of 100 Hz. Above and below this region the thresholds for cochlear nucleus units increase at an average rate of about 4 dB/octave (Glass, 1983). Slopes of auditory nerve fibers increase at a similar or slightly lower rate (Kiang and Moxon, 1972). The slopes of the neural threshold contours above 100 Hz, indicated by the sloping range bars for g and k in Fig. 7, are similar to the slopes of the behavioral threshold contours above 500 Hz, but are much shallower than the slopes of most if not all of the behavioral threshold contours in the 100 Hz to 500 Hz region. Furthermore, the behavioral threshold contours seldom rise as a function of decreasing frequency below 100 Hz as the neural tuning curves do. This suggests that some neural mechanism other than rate of discharge in single auditory neurons is involved in the detection of sinusoids in this frequency range, though once again questions of sampling bias, threshold definition, etc. must be considered.

Frequency discrimination

I will now turn to single-unit studies of frequency following in electrically stimulated auditory neurons and their relation to psychophysical studies of frequency discrimination. Investigators in several laboratories have found that neurons in the auditory periphery follow the frequency of sinusoidal electrical stimulation very well, perhaps better than they follow acoustic sinusoids (Hartmann et al., 1984; Glass, 1984). Hartmann has found that synchronization indices for electrical stimuli are on the average higher than those reported for acoustic stimuli by Johnson (1980) at almost all frequencies tested from 100 Hz to 3 kHz (Hartmann, personal communication). This remarkably good frequency following behavior of auditory neurons contrasts markedly with the very poor frequency discrimination behavior of the organism (Figs. 5 and 6). This discrepancy suggests that the temporal information at the auditory periphery is not in a form which can be utilized by higher levels in the auditory pathway. Analyses such as Siebert's (1970) have indicated that the auditory nerve's frequency following even to acoustic stimulation is much better than would be predicted by frequency discrimination performance. This suggests that the auditory nerve may not be the most appropriate level to analyze the neural encoding of temporal information relative to perception. It is well known that temporal encoding (frequency following) deteriorates as the encoded information ascends the auditory pathway (Rouiller et al., 1979). At higher centers, the neural data might more closely match psychophysical performance (see Merzenich et al., 1973). Alternatively, this temporal information may become translated to a place code or other code at these centers, but the requirement of matching the neural limits to the psychophysical
limits still applies. Given the reasonably close match between human and nonhuman primate performance on nonspectral frequency discrimination tasks, monkeys and possibly other animals as well, should serve as reasonable animal models to study the neural mechanisms of nonspectral pitch. Combined neural and psychophysical observations in the same subject would be an ideal model, providing the best index of the appropriate level of stimulation for the neural studies and providing the most unambiguous comparisons between the neural and behavioral measures.

Conclusions

The considerable overlap in results of psychophysical studies from implanted human and nonhuman primates suggests that the monkey is a good model for experimental studies applicable to humans. Whether or not this conclusion can be extended to other nonhuman mammals remains to be demonstrated. If neural data from animal studies are to be applied to humans, the discrepancies between the neural and psychophysical thresholds reported in the literature must be resolved. This can best be done by simultaneous psychophysical and neurophysiological studies in the same animal subjects. Such an experimental model would be ideal for assessing the validity of encoding models based on neural data. This powerful psychophysical-neural animal model applied to clinical problems should lead to significant advances in otolaryngology.

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References


