Electrical Cochlear Stimulation in the Deaf Cat: Comparisons Between Psychophysical and Central Auditory Neuronal Thresholds

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Introduction

Electrical stimulation of the auditory nerve has led to restoration of speech perception in many profoundly deaf patients using cochlear prostheses (cf. Dorman 1993 for review). Currently cochlear prostheses provide auditory capacity in several thousand otherwise deaf adults, and cochlear implants are recognized also as a prosthetic option for some profoundly deaf children (Boothroyd et al. 1991; NIH Consensus Statement 1995). The successful application of cochlear prostheses raises important issues concerning information processing in the auditory system, and the phenomenon of electrical hearing has stimulated substantial research toward understanding the basic mechanisms that make this kind of hearing possible (cf. Raggio and Schreiner 1994; Shannon 1993 for reviews).

An issue of fundamental importance in electrical hearing is the absolute threshold for activation of the surviving spiral ganglion cells in the deaf cochlea. Adequate stimulation of the auditory nerve array activates central auditory pathways and is therefore an antecedent condition for perception in electrical hearing. Several animal models have been developed that afford the opportunity to study behavioral and physiological variables in the same deaf animals (Beitel et al. 1993, 1995, 2000; Montney et al. 1998; Smith et al. 1994). Although these models have yet to be exploited systematically, initial published results have shown that electrical auditory brain stem responses (EABRs) and behavioral detection thresholds are similar for a variety of monopolar and bipolar cochlear electrode configurations in the cat (Smith et al. 1994).

Since the publication of a seminal report on electrical hearing that explored relationships between psychophysical phenomena measured in humans with neural responses measured in cats (Merzenich et al. 1973), several investigators have indirectly compared behavioral thresholds with responses in single auditory nerve fibers evoked by electrical cochlear stimulation. When psychophysical detection thresholds (measured in macaque monkeys and humans) were compared with afferent fiber thresholds (measured in cats or squirrel monkeys), investigators reported that the neural thresholds were typically higher than the behavioral thresholds (Moon et al. 1993; Parks and Colombo 1987; Püngst 1988, 1990a; Püngst et al. 1991; Shannon 1989). No one, of course, suggested that psychophysical detection can occur at stimulus amplitudes that are below those required to activate auditory nerve fibers. The apparent paradox has been ascribed instead to confounding by experimental differences between species, types of electrodes, animal models, modes of stimulation, duration of deafness, definitions of threshold, and other factors when indirect com-
parisons are made across research groups (Pfingst 1988). Several preliminary reports have demonstrated that behavioral and neurophysiological thresholds are similar when measured in the same animals (Beitel et al. 1993, 1995, 2000; Montney et al. 1998; Pfingst et al. 1998).

To evaluate the effects of perceptually significant electrical cochlear stimulation on the central auditory system, we have developed a feline behavioral model that allows us to obtain psychophysical and neurophysiological data from the same cat (Beitel et al. 1995). In the experiments described in the following text, bursts of short phase duration pulses (0.2 ms/phase) were used to obtain psychophysical thresholds in cats implanted with bipolar scala tympani electrodes or monopolar round window electrodes. In acute physiological experiments at the conclusion of behavioral testing, thresholds were determined for neurons in the inferior colliculus and the primary auditory cortex in trained animals, and the cochleae were prepared subsequently for histological analysis. Psychophysical thresholds then were compared with neurophysiological thresholds and with cochlear histopathology in the same cats.

METHODS

The general experimental protocol for the present study involved three stages. First, animals were deafened neonatally, and an electrode was implanted for electrical stimulation at the left cochlea. As required for a series of ongoing studies (cf. Leake et al. 1991; Snyder et al. 1995), a regimen of chronic electrical stimulation was initiated during this stage. Summaries of the implantation and chronic stimulation histories for each of the trained deaf cats n = 10) are provided in Table 1. Second, the animals were trained to detect biphasic electrical pulses applied to the cochlea, and their detection thresholds were estimated psychophysically. In some subjects, chronic stimulation in addition to the behavioral training was continued during this stage of the study. Finally in acute electrophysiological experiments, neural thresholds for electrical pulses were recorded in the right inferior colliculus (IC) and the right primary auditory cortex (A1) with tungsten microelectrodes.

This report is based on data obtained from 10 deaf cats. Nine kittens were deafened neonatally, and one cat was deafened during adulthood (Table 1). Pertinent data are included from an electrophysiological experiment in a chronically stimulated deaf kitten (K101) that was not behaviorally trained for this study. Also psychophysical thresholds are reported for two normal hearing cats (1 adult and 1 kitten) that were trained and tested on the detection task using acoustic stimuli. Several procedures used in this study have been described in detail elsewhere (Leake et al. 1991; Raggio and Schreiner 1994; Rebscher 1985; Snyder et al. 1995; Vollmer et al. 1999) and will be repeated here in a condensed form. All procedures followed National Institutes of Health guidelines for care and use of laboratory animals.

Preexperimental procedures: deafening, cochlear implantation, and chronic stimulation

Kittens were deafened by daily intramuscular injections of neomycin sulfate for 16–21 days after birth; the adult cat was deafened by subcutaneous coadministration of kanamycin and aminoxyacetic acid (Leake et al. 1987, 1991). As evaluated by click-evoked auditory brain stem responses and frequency-following responses to a tonal stimulus (Snyder et al. 1990), hearing thresholds in the sedated animals were >110 dB sound pressure level (SPL re 20 µN/m²) before implantation.

Cochlear electrodes (Fig. 1) were fabricated from Teflon-coated platinum-iridium (90–10%) wires embedded in a silicone rubber carrier (Rebscher 1985) and were implanted using sterile surgical procedures. Before all surgical procedures an animal was sedated (ketamine: 22–33 mg/kg; acepromazine maleate: 0.1 mg/kg), and anesthesia was induced by pentobarbital sodium (7–10 mg/kg) delivered via an intravenous catheter. A surgical level of anesthesia was maintained by intravenous infusion of pentobarbital sodium in Ringer solution. In three kittens (K80, K82, and K90), and in the adult cat (CH332), a monopolar round window electrode and ground lead were implanted so that a 400-µm-diam ball at the stimulation end of the active lead was located adjacent to the round window membrane in CH332 and K90 or just inside (1–2 mm) the round window in K80 and K82 (Leake et al. 1995). The ground lead was located under the temporalis muscle. In six kittens (K83, K84, K85, K86, K93, and K94), a feline intracochlear electrode array consisting of four bipolar contacts (250-µM diam) arranged as two offset-radial pairs was implanted in the scala tympani (Leake et al. 1991). In K84 a broken wire made it necessary to use an apical-basal pair (contacts 1,3) for stimulation; otherwise all intracochlear electrical stimuli were delivered to apical pairs located 9–11 mm from the round window (Fig. 1; contacts 1,2).

Psychophysical procedures

Training was initiated for the nine deaf kittens at a median age of 22 wk (min/max = 17/28 wk) using a paradigm for conditioned avoidance responses (CAR) (Heffner and Heffner 1985). During training, the cat was placed in a wire cage (56 × 33 × 33 cm) located inside an acoustical chamber (Industrial Acoustics) that was lined with 7.6-cm acoustic foam. The cat was trained to lick a metal spoon located at one end of the wire cage to obtain a preferred food reward.

### TABLE 1. Chronic stimulation histories

<table>
<thead>
<tr>
<th>Cat</th>
<th>Age at Surgery, wk</th>
<th>Age at Initial Stimulation, wk</th>
<th>Stimulus Amplitude, µA&lt;sub&gt;p&lt;/sub&gt;</th>
<th>Stimulation Period, wk</th>
<th>Type of Stimulus</th>
<th>Age at Death, wk</th>
<th>Behavioral-Death Interval, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monopolar stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH332</td>
<td>Adult</td>
<td>6.8</td>
<td>7.0*</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>K90</td>
<td>6.8</td>
<td>7.0*</td>
<td>80</td>
<td>30 pps</td>
<td>30 pps</td>
<td>30 pps</td>
<td>30 pps</td>
</tr>
<tr>
<td>K80†</td>
<td>5.7</td>
<td>6.4</td>
<td>300–315</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>K82‡</td>
<td>5.8</td>
<td>6.4</td>
<td>400–315</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>Bipolar stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K83</td>
<td>6.0</td>
<td>10.5*</td>
<td>125</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>K84</td>
<td>7.5</td>
<td>10.0</td>
<td>200–400</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>K85</td>
<td>7.0</td>
<td>10.0</td>
<td>125</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>K86</td>
<td>6.0</td>
<td>9.0*</td>
<td>30–160</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>K93</td>
<td>7.0</td>
<td>8.0</td>
<td>40–400</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
<tr>
<td>K94</td>
<td>7.0</td>
<td>8.0</td>
<td>40–500</td>
<td>515</td>
<td>515</td>
<td>515</td>
<td>515</td>
</tr>
</tbody>
</table>

* Device failed and animal was reimplanted before behavioral testing. † Monopolar electrode located inside the round window. ‡ Backpack speech processor.
(meat puree). Contact with the spoon was monitored by a computer (sampling rate = 50 Hz), and the puree was delivered at a constant rate from a motor-driven syringe pump (Thompson et al. 1990) during periods when the cat was licking the spoon. On warning trials, a warning signal or conditioned stimulus (CS) was presented, and the cat was required to interrupt licking to avoid a mild electrocutaneous shock or unconditioned stimulus (UCS). The UCS was a 140- to 210-ms-duration sinusoidal pulse train (60 Hz), adjusted for each cat to the minimum current intensity (≈0.5–2.0 mA) required to maintain avoidance behavior.

For the deaf animals, the CS was a train of biphasic rectangular-wave current pulses (charge-balanced; 0.2 ms/phase). The pulses were computer generated (National Instruments LabView) at a predetermined pulse rate (pulses/s or pps) and then conducted through an audio attenuator (HP 350B) to an optically isolated constant current stimulator (Vureck et al. 1981). The output from this stimulator was delivered to an implanted cochlear electrode through a percutaneous cable. Before each behavioral session, this system was calibrated to a reference level of 0 dB relative to 1 mA pp; this calibration applies to all psychophysical and neurophysiological thresholds reported in the following text in the deaf cats.

For the two normal hearing cats, acoustic stimuli were 2-s-duration tones (rise-fall = 10 ms). The CS was conducted through an audio attenuator (HP 350B) to a tail-end amplifier (McIntoch) and then to a crossover network consisting of midrange and high-frequency speakers (Realistic 40-1996A and Realistic 40-1377, respectively). This system was calibrated with a sound level meter (Brüel and Kjaer 2209) and a spectrum analyzer (NCS UA-500A) with the microphone (Brüel and Kjaer 4134) positioned at the approximate location of a cat’s head during psychophysical testing. The system was essentially flat (±1 dB-A) over the range from 250 Hz to 20 kHz, and all second and third harmonics were ≥50 dB below fundamental frequencies at octave intervals from 250 Hz to 32 kHz.

The CAR paradigm is depicted schematically in Fig. 2A. During a training session, 80% of the trials were 2-s-duration safe trials followed by a 1-s-duration intertrial interval. On safe trials, CSSs and UCSs were not presented. The remaining 20% of trials were 2-s-duration warning trials. On these trials, the CS was presented at a suprathreshold intensity, and an electric shock or UCS was applied to the cat’s tongue at the end of a warning trial if the cat was in contact with the spoon. A light located above the spoon was turned on and off simultaneously with the UCS to provide visual feedback for successful avoidance. To avoid the UCS, the cat was required to break contact with the spoon during the 2-s trial duration and to refrain from licking the spoon until the light was turned off. Each warning trial was followed by a 1-s-duration intertrial interval. Warning trials occurred randomly during a session, with the restriction that they could not occur successively. After several suprathreshold warning trials, the cats typically avoided the noxious UCS by breaking contact with the spoon during the CS. The intensities of the CS then were reduced gradually over several training sessions. Once performance stabilized from session to session, threshold testing was begun.

To estimate threshold performance, the method of limits (MOL, descending series) and the method of constant stimuli (MCS) were used (Table 2). With the MOL, on three successive warning trials the CS was presented at a constant suprathreshold level. In the next block of three warning trials, the level of the CS was reduced by 1- (electrical) or 3 dB (tonal), and this procedure was repeated until the cat failed to detect two of three warning signals. The level of the CS then was increased to a suprathreshold level, and the procedure was repeated. With the MCS, the CS was presented randomly during a session within a range (5–7 dB, 1-dB steps) that bracketed the estimated threshold. The minimum difference between successive CS presentations was a 1-dB step. During a testing session, the pulse rate of electrical stimuli (range: 2–100 pps) or the frequency of acoustic stimuli (range: 0.25–16.0 kHz at octave intervals) was constant; only the amplitude of the CS was varied. Exemplary data for a deaf animal tested with pulse rates >100 pps also are included in this report (Fig. 4A). Testing was continued until threshold performance from session to session was within 2 dB for electrical pulses or within 3 dB for tones.

At the conclusion of testing, the following response measures were obtained by pooling data from three to five testing sessions: 1) false alarm rate: p(FA). False alarms (FAs) occurred whenever a cat was not in contact with the spoon during the final 200 ms of a safe trial. The p(FA) was calculated by p(FA) = total FA/total safe trials. 2) Hit rate at each level of the CS: p(H). Hits occurred whenever a cat was not in contact with the spoon during the final 200 ms of a warning trial, i.e., whenever a cat successfully avoided the UCS. The p(H) was calculated separately for each intensity of the CS by p(H) = total avoidance responses at each level of the CS/total warning trials at each level of the CS. A correction based on p(FA) was calculated (Green and Swets 1966) to obtain the probability for detection at each
level of the CS: $p(\text{DETECTION}) = p(H) - p(\text{FA})/1 - p(\text{FA})$.

3) Median reaction time (MRT) at each level of the CS. Reaction time (RT) is defined as the time between onset of the CS and interruption of licking.

Figure 2B illustrates typical psychometric and MRT functions in a deaf cat (K90). The abscissa shows the levels of the CS in dB. The 50% avoidance threshold was estimated by interpolation (arrow) from the dashed line that represents $p(\text{DETECTION}) = 0.5$.

### Table 2. Data summary

<table>
<thead>
<tr>
<th>Cat</th>
<th>Group/Method</th>
<th>Electrode</th>
<th>Percent Ganglion Cells</th>
<th>Behavioral Thresholds</th>
<th>Neural Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 pps (dB)</td>
<td>2 pps (dB)</td>
</tr>
<tr>
<td>CH332</td>
<td>Re/MOL</td>
<td>RW</td>
<td>10.6</td>
<td>45.3</td>
<td>184 (44)</td>
</tr>
<tr>
<td>K90</td>
<td>Re/MCS</td>
<td>RW</td>
<td>42.7</td>
<td>44.9</td>
<td>172 (29)</td>
</tr>
<tr>
<td>K80</td>
<td>Ri/MOL</td>
<td>RW</td>
<td>47.8</td>
<td>37.2</td>
<td>70 (29)</td>
</tr>
<tr>
<td>K82</td>
<td>Ri/MOL</td>
<td>RW</td>
<td>48.5</td>
<td>45.3</td>
<td>172 (31)</td>
</tr>
<tr>
<td>K83</td>
<td>Bi/MCS</td>
<td></td>
<td>69.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K84</td>
<td>Bi/MCS</td>
<td></td>
<td>54.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K85</td>
<td>Bi/MCS</td>
<td></td>
<td>62.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K86</td>
<td>Bi/MCS</td>
<td></td>
<td>39.1</td>
<td>31.9</td>
<td>40 (23)</td>
</tr>
<tr>
<td>K93</td>
<td>Bd/MCS</td>
<td></td>
<td>25.3</td>
<td>45.3</td>
<td>184 (23)</td>
</tr>
<tr>
<td>K94</td>
<td>Bd/MCS</td>
<td></td>
<td>30.3</td>
<td>44.4</td>
<td>166 (28)</td>
</tr>
</tbody>
</table>

Thresholds are expressed in dB (re: 0 dB = 1 μA<sub>pp</sub>) and μA<sub>pp</sub>. Under Behavioral Thresholds, numbers in parentheses show mean number of trials at each stimulus intensity used to estimate thresholds. Numbers in parentheses under Neural Thresholds show the number of thresholds recorded in the inferior colliculus (ICC) and the primary auditory cortex (A1). The four experimental groups are Re, round window, extracochlear; Ri, round window, intracochlear; Bi, bipolar, damaged; MOL, method of limits; MCS, method of constant stimuli. * Auditory cortex damaged in K94, K94, 100 pps. Percent Ganglion Cells refers to surviving fraction of cells in the electrically stimulated spiral ganglion.
EABRs were recorded in sedated animals (ketamine: 22–33 mg/kg; acepromazine maleate: 0.1 mg/kg) with silver wires inserted through the skin over the vertex (active electrode), below the left stimulated ear (reference electrode), and under the right pinna (ground electrode). Electrical pulses (20 pps) were delivered over a range of intensities in 2-dB steps, and at each intensity, responses were differentially amplified (100,000 times), band-pass filtered (100 Hz to 3.0 kHz), and averaged for 500 repetitions of the stimulus. This procedure was repeated, and the waveforms were added to enhance the signal to noise ratio. From a visual display of the EABR waveforms, two experienced observers independently estimated EABR thresholds as the minimum intensity step that produced a reliable auditory response (typically Wave IV) within a 5-ms recording window. [Wave IV, the largest amplitude wave of the acoustically evoked brain stem response in the cat can be well defined in the EABR waveform as well and is most suitable for measurement of “threshold” responses (cf. van den Honert and Stypulkowski 1986).] If the observers’ estimates did not agree, the procedure was repeated in steps of 1 dB.

Spread of current to nonauditory structures during electrical cochlear stimulation, especially extracochlear round window stimulation, can produce motor responses by stimulation of the facial nerve or the muscle overlying the return electrode (Hartmann et al. 1984). To evaluate this potential source of cues for psychophysical detection of electrical cochlear stimulation, thresholds were determined for twitching movements of facial muscles during EABR recording sessions in the cats implanted with an extracochlear round window electrode (CH332 and K90). Electromyographic activity (EMG) accompanied by twitching movements of the facial muscles occurred only at stimulus levels that were much higher than EABR (>5–10 dB) or psychophysical (>8–15 dB) threshold levels. These results suggest that overt motor responses and associated somatosensory cues were not produced at the levels of electrical stimulation used to estimate behavioral and EABR thresholds.

At the conclusion of behavioral testing, a cat was prepared for an acute physiological experiment. The animal was sedated, and anesthesia was induced and maintained by intravenous infusion of pentobarbital sodium in Ringer solution (cf. preceding text for details). The IC or the A1 contralateral to the cochlear implant was then exposed surgically. In most of the experiments the IC was studied before surgically exposing the cortex. When the temporal order of the surgeries and recording procedures was reversed, there was no apparent order effect on the quality of recordings in either the IC or the A1.

For electrophysiological recording in these central auditory structures, biphasic pulses were generated by a microprocessor (TMS32010, 16-bit D-A converter at 60 kHz) and were delivered serially to an audio attenuator, to an optically isolated constant current stimulator, and then to the cochlear implant electrodes through an electrode selector switch. Before each experiment, this system was calibrated to a reference level identical to the calibration used in the behavioral experiments (0 dB = 1.0 μA/m). During an experiment, pulse amplitude was varied manually (1-dB step); pulse rate (pps) and pulse train duration were controlled by a computer.

Tungsten microelectrodes (0.8–2.5 MΩ at 1 kHz) were used to record responses of single neurons and multineuronal clusters in the IC and the A1 in each cat. Neuronal units were identified in background noise using a search stimulus (biphasic current pulses; 0.2 ms/phase) delivered at a pulse rate of 2–3 pps. Responses were amplified (10,000–20,000 times) and band-pass filtered (300 Hz to 3.0 kHz) and, for quantitative analyses, neuronal spikes were isolated from background noise with a window discriminator (BAK DIS-1). The time of occurrence of each discriminated spike was recorded and stored in a computer. From responses to pulse trains, poststimulus time histograms (PSTHs) were constructed and used in analyses of neuronal temporal discharge patterns.

Electrode penetrations in the IC were aligned orthogonal to the cochleotopic organization of the central nucleus, and threshold responses were recorded at 100-μm intervals as the electrode advanced along a dorsomedial to ventrolateral trajectory. Two to four complete penetrations were obtained in each experiment. The border between the central nucleus (ICC) and the more superficially located external nucleus (ICE) is a fibrous layer characterized by thresholds that are higher than those recorded in either nuclei (Snyder et al. 1990). Neurons in the ICC, recorded before the electrode entered this high-threshold layer, are not included in the present study.

In the cortical experiments, threshold responses were recorded at intracortical depths of 600–1,200 μm (layers 3 and 4) with each penetration orthogonal to the surface of the cortex. In each experiment, penetration locations separated by ~500 μm were selected so that the cortical threshold map at the conclusion of the experiment consisted minimally of an anterior-posterior line of penetrations (orthogonal to the isofrequency axis of A1) and a dorsoventral line of penetrations (parallel to the isofrequency axis of A1). The number of thresholds recorded in the A1 and the ICC are tabulated separately for each of the trained animals in Table 2.

Comparison of behavioral and neurophysiological thresholds

An important objective of this study was to compare psychophysical thresholds with neurophysiological thresholds obtained in the same animals. To estimate the neural threshold at a recording location, biphasic current pulses (0.2 ms/phase) were delivered in 1-dB steps at a slow rate (2 pps) to enhance detection of threshold neuronal activity in background noise. The stimulus intensity just sufficient to activate the neuron(s) was determined using audiovisual criteria based on careful monitoring of the response on an oscilloscope and an audio monitor. Thus at the stimulus threshold intensity each pulse produced a response 50–75% of the time; however, there was no neuronal response when the intensity of the pulses was reduced by 1 dB. For comparisons with psychophysical data obtained from a particular cat, the lowest neuronal thresholds in the ICC and the A1 were defined as the minimum stimulus intensities that evoked responses, as determined by analysis of data from all recording locations in each of these central auditory structures in the same cat.

In this study, the pulse rates used to estimate neural thresholds (2 pps) and behavioral thresholds (2–100 pps) were usually not identical. The differences in rates have an important effect on the comparisons between behavioral and neural thresholds reported below. Given our criterion for defining ICC and A1 thresholds, stimulus rate was not a factor in neural threshold estimation because the stimulus intensity at threshold does not change when the pulse rate is varied. However, over the range of rates used in this study to estimate behavioral thresholds, a 1- to 2-dB decrease in thresholds can be expected as a function of pulse rate for short phase duration pulses (Moon et al. 1993; Shannon 1985). Our measure of neural threshold does not include a rate factor, whereas the behavioral thresholds estimated at pulse rates ≥30 pps may involve neural mechanisms that are dependent on pulse rate. This issue is addressed in greater detail in the analyses presented in Fig. 9 and DISCUSSION.

Spiral ganglion cell morphometry

At the conclusion of the electrophysiological experiments, the cochleae were preserved by perilymphatic and transcerebral perfusions, and cochlear specimens containing the organ of Corti and the spiral ganglion were prepared according to procedures described previously (Leake and Hradek 1988; Leake et al. 1991, 1995). A morphometric analysis (mean volume ratio) was performed to quantify the mean density of surviving spiral ganglion cell somata in Rosenthal’s canal relative to the mean density observed in normal hearing cats. The pattern and severity of ganglion degeneration for the neonatally deafened kittens have been reported previously (Leake et al. 1995, 1999). For each stimulated ear in the present study, values...
for all cochlear regions were averaged to determine the overall mean, expressed as percent of normal. These data were used to compare nerve cell survival in the stimulated cochlea with psychophysical and neurophysiological thresholds obtained in the same deaf cats.

**RESULTS**

**Basic psychophysics**

The CAR paradigm usually includes food or water deprivation as a standard procedure to motivate a licking response (Heffner and Heffner 1985, 1988). In the present study, nine of the deaf animals and one normal hearing animal were kittens or juvenile cats during the period of behavioral training and testing, and because restricting their diet might have impaired normal growth and development, dry food and water were available ad libitum in their home cages. In spite of this necessary adaptation, the psychophysical results described in this section indicate that the CAR paradigm was a valid and reliable choice for training and testing young deaf and normal hearing cats.

**ACOUSTIC THRESHOLDS IN NORMAL HEARING CATS.** To establish a reference level or standard for evaluation of performance in the CAR paradigm, thresholds were estimated (MOL) in two normal hearing cats using tonal stimuli. The results are shown in Fig. 3A. The two curves in the figure are mean threshold audiograms based on the average performance of normal hearing cats in two different studies (Fay 1988); according to Fay, these average audiograms bracket the mean hearing range for normal hearing cats. For the two normal hearing cats in the present study (adult, •; juvenile, ○), 50% avoidance thresholds obtained at each frequency tested are distributed near the mean normal audiograms shown in Fig. 3A. The results indicate that acoustic detection thresholds obtained in our laboratory are consistent with those reported by other investigators. We assume, therefore, that the thresholds reported in the fol-
lowing text for deaf animals are based on valid conditioned avoidance procedures.

**FA RATE.** The FA rate provides information that reflects the influence on performance of an animal’s “pausing” strategy. In general, a low FA rate indicates that performance is under stimulus control, and a correction for pauses may be applied to obtain threshold estimates. Figure 3B shows the distribution of FA rates for all threshold testing sessions with 0.2-ms/phase biphasic pulses. The mean number of safe trials per session was 222 ± 48.7 trials (mean ± SD); the median FA rate was 9.3% (average absolute deviation: 4.1%). This FA rate compares favorably with FA rates reported for normal hearing, adult cats tested in a CAR paradigm (Heffner and Heffner 1985).

**STABILITY ACROSS SESSIONS.** In the deaf cats, psychophysical thresholds were relatively stable over the period of time required for behavioral testing. In two animals (K93 and K94), elevation of EABR thresholds was observed a few weeks before training was initiated. These animals may have experienced stimulation induced damage to the cochlea and spiral ganglion neurons caused by EABR testing with a faulty stimulator. In these animals, EABR thresholds stabilized at new levels and remained stable over the ensuing periods of behavioral testing. Figure 3C shows psychophysical thresholds in one of these cats (K94) during a period of behavioral testing when EABR thresholds had stabilized at the higher level. The results show stable performance across 10 consecutive daily testing sessions (weekends excepted) at each pulse rate (2 and 30 pps), representing a total testing period of ~1 mo. The mean psychophysical thresholds for 0.2-ms/phase biphasic pulses delivered at 2 and 30 pps were 45.3 ± 1.0 dB and 44.4 ± 1.0 dB, respectively.

**PSYCHOPHYSICAL DETECTION THRESHOLDS.** On the basis of data pooled from three to five testing sessions, reliable threshold estimates were obtained in all cats tested with 0.2-ms/phase biphasic pulses. Thresholds were obtained by interpolation from psychometric functions that were usually quite steep (cf. Fig. 2B), with 25–75% detection scores occurring within a range of 2 ± 0.67 dB. The threshold data summarized in Table 2 include for each cat the mean number of trials at each stimulus intensity used to produce psychometric functions; thresholds extend from a low of 29.4 dB (30 μA_{pp}) to a high of 47.4 dB (236 μA_{pp}), a range of 18 dB.

**PULSE RATE.** The exemplary data shown in Fig. 4A illustrate a trend observed in every case for stimulation with biphasic pulses at different pulse rates: as pulse rate increases, there is a monotonic decrease in psychophysical thresholds. Over a range of pulse rates from 30 to 1,000 pps, the thresholds depicted in Fig. 4A decrease by 2.9 dB. Note that the interpulse interval (IPI) also varied with the pulse rate: IPI = [(1,000/ pps) − pulse duration]. Psychophysical thresholds were obtained at two pulse rates (2 and 30 pps) in four of the cats included in Table 2. The results are summarized in Fig. 4B. In each cat, the threshold was lower at the higher pulse rate, and the absolute mean difference (35 μA_{pp}) was significant (paired t = 4.684; df = 3; P < 0.02).

**REACTION TIME.** On warning trials, the latency or RT between onset of the warning signal (CS) and interruption of licking was recorded. Figure 4C shows MRTs in a cat (K94) as a function of stimulus levels near threshold for pulsatile stimuli delivered at rates of 2 and 30 pps. Two features of the illustrated functions are noteworthy. First, although a 2-s interval separated the onset of the CS from the onset of the noxious stimulus (UCS), the cat usually interrupted licking within 1 s after the onset of the CS when the CS was suprathreshold. For a pulse rate of 2 pps, MRTs at suprathreshold levels are <500 ms, indicating that the cat usually interrupted licking before the occurrence of the second pulse. A second feature is that MRTs to pulses delivered at a rate of 2 pps are faster than those delivered at a rate of 30 pps. However, the psychophysical thresholds at 2 pps are higher than the psychophysical thresholds at 30 pps for K94, i.e., stimulus intensities at 2 pps are higher than those delivered at 30 pps (Fig. 3C). When MRTs recorded in the four cats tested at 2 and 30 pps were compared at equal stimulus intensities, the results shown in Fig. 4D were obtained: Mean MRT for the four animals is faster at a pulse rate of 30 pps. The mean difference (410 ms) between the two rates is statistically significant (t = 3.625; df = 11; P < 0.005).

**Comparisons of psychophysical and neural response thresholds**

To facilitate comparisons between psychophysical thresholds and physiological thresholds, each of the deaf cats was assigned a posteriori to one of four groups (Re, Ri, Bi, or Bd) that are distinguished from one another by a combination of conditions that is unique for each group. Psychophysical thresholds are relatively homogeneous within each group (Table 2). For the cats in group Re (CH332 and K90: Re = round window, extracochlear), stimuli were delivered by round window, extracochlear monopolar electrodes. For the 30-pps stimulus, the average behavioral threshold and the threshold difference for the two cats are 45.1 and 0.4 dB, respectively. In group Ri (K80 and K82: Ri = round window, intracochlear), the monopolar stimulating electrodes were located just inside the round window membrane (Leake et al. 1995). At a pulse rate of 30 pps, the average behavioral threshold is 37.9 dB and the threshold difference between the two cats is 1.4 dB. The cats in group Bi (K83, K84, K85, and K86: Bi = bipolar, intracochlear) were stimulated at different pulse rates (80, 100, 80, and 30 pps, respectively) with intracochlear bipolar electrodes. Mean behavioral threshold is 32.0 dB and thresholds in this group are within 5.2 dB. The cats in group Bd (K93 and K94: Bd = bipolar, damaged cochlea) also were stimulated with intracochlear bipolar electrodes. As noted above, however, post mortem histological analyses suggested that EABR testing with a faulty stimulator may have induced damage to the cochlea and spiral ganglion neurons in these cats, resulting in elevated psychophysical detection thresholds. For the 30-pps stimulus, the mean behavioral threshold is 44.8 dB and the threshold difference between the two cats is 0.9 dB.

The numbers of neural thresholds recorded in the ICC and the A1 are tabulated separately for each of the trained animals in Table 2. In the cats implanted with a monopolar stimulating electrode (groups Re and Ri), 446 thresholds were recorded (ICC: n = 318; A1: n = 128). The number of neural thresholds obtained in the cats implanted with bipolar scala tympani electrodes (groups Bi and Bd) was 418 (ICC: n = 252; A1: n = 166).
EABR AND PSYCHOPHYSICAL THRESHOLDS. Figure 5A illustrates a representative example of EABR waveforms evoked in a neonatally deafened cat (K93) by biphasic current pulses (0.2 ms/phase; 20 pps). Stimulation was delivered with a bipolar scala tympani electrode in 2-dB steps from 46.0 (126 μA pp) to 60.0 dB (1 mA pp). Each waveform is the averaged response to 500 repetitions of the stimulus. For convenience in viewing the waveforms, Waves I–IV are identified on the bottom trace according to a response latency criterion (van den Honert and Stypulkowski 1986). On the basis of independent estimates by two experimenters (cf. METHODS), the EABR threshold (↓) in this cat was 50.0 dB.

EABR measurements were made to maintain appropriate stimulus intensities during periods of chronic stimulation (Leake et al. 1991, 1995); in each of the neonatally deafened cats, EABR thresholds (Table 2) were obtained within 2.2 ± 1.8 wk of psychophysical testing. The mean time required for behavioral threshold estimation was 1.6 ± 0.7 wk. In six animals, EABR thresholds were measured either during the period of behavioral testing or EABR measurements obtained before and after behavioral testing were identical. In the three remaining neonatally deafened animals, the reported EABR threshold was measured within 1.5 ± 0.9 wk of behavioral testing. The adult cat (CH332) was not stimulated chronically, and the EABR threshold in this animal was measured at the time of the acute physiological experiment.

In Fig. 5B, the psychophysical threshold (pulse rates = 30–100 pps) is plotted against the EABR threshold (pulse rate = 20 pps) for each animal in the four groups. There is a clear tendency toward clustering by groups. The cats in groups Re and Bd are clustered at high psychophysical and EABR thresholds, psychophysical and EABR thresholds are lowest for the cats in group Bi, and thresholds for the cats in group Ri show values intermediate to thresholds obtained in the other groups. The two threshold measures are significantly correlated for the combined groups (n = 10; r = 0.97; P < 0.001). Moreover, the data points are located below the diagonal line,
indicating that psychophysical thresholds were lower than EABR thresholds in all of the cats. For within-cat comparisons, the mean threshold difference (neural-psychophysical) is 6.5 ± 2.1 dB ($t = 9.83; df = 9; P < 0.001$).

**THRESHOLDS FOR INTRACOCHLEAR BIPOLAR STIMULATION.** In four cats implanted with intracochlear bipolar electrodes (K83 and K86, group Bi; K93 and K94, group Bd), 14 within-cat comparisons of psychophysical thresholds (2 pps, $n = 6$; 30 pps, $n = 6$; 80 pps, $n = 2$) with minimum neural thresholds (2 pps) were obtained; in six comparisons, the neural thresholds were lower than the behavioral thresholds (Table 2). Figure 6, A–C, compares minimum ICC and A1 thresholds evoked at a pulse rate of 2 pps with psychophysical thresholds estimated at pulse rates of 2 and 30 pps in three cats (K86, K93, and K94). In Fig. 6, A–C, - - - represents the EABR threshold (20 pps) measured in each of these animals. The threshold data for K83, which was tested behaviorally at only one pulse rate (80 pps), are not included in Fig. 6. In cats K86 (Fig. 6A) and K93 (Fig. 6C) minimum neural thresholds are below the behavioral thresholds estimated at 2 pps. The A1 in cat K94 was damaged during surgery (Table 2*) before the cortical recording experiment. The injury probably accounts for the reduced sensitivity and higher minimum threshold seen in the cortex of this particular animal. In cat K93 minimum neural thresholds are also below the behavioral threshold estimated at 30 pps.

The differences (neural-psychophysical) for mean EABR, ICC, and A1 thresholds compared with mean psychophysical thresholds at 2 and 30 pps are summarized in Fig. 6D. Mean EABR thresholds are 2.9 and 5.5 dB higher than mean psychophysical thresholds at pulse rates of 2 and 30 pps. Mean minimum ICC and A1 neural thresholds are 1.1 dB more sensitive than the mean psychophysical threshold at 2 pps and 1.5 dB less sensitive than the mean psychophysical threshold at 30 pps. However, these small differences between mean minimum neural thresholds and mean psychophysical thresholds were not significant (both $P > 0.05$).

**THRESHOLDS FOR MONOPOLAR ROUND WINDOW STIMULATION.** In the four cats implanted with monopolar round window electrodes (groups Re and Ri), 10 within cat comparisons of psychophysical thresholds (2 pps, $n = 2$; 30 pps, $n = 8$) with minimum neural thresholds (2 pps) were possible; in all comparisons the neural thresholds were higher than the behavioral thresholds. Figure 7 shows data for these cats (CH332 and K90, group Re; K80 and K82, group Ri), and compares psychophysical thresholds estimated for biphasic pulses delivered at a rate of 30 pps with minimum ICC and A1 neural thresholds for pulsatile stimuli (0.2 ms/phase; 2 pps). Although the ICC threshold was within 3.5 dB of the behavioral threshold in two cats, the psychophysical threshold was lower than the average of the minimum ICC and A1 neural thresholds in each cat (overall mean difference = 6.5 ± 2.2 dB; $t = 4.89; df = 3; P < 0.02$).

**Responses of ICC neurons to trains of pulses**

Typically, ICC neurons stimulated at suprathreshold levels (3–5 dB above threshold) followed low-frequency pulse trains (e.g., 10–30 pps) in a sustained manner, i.e., the neurons responded to each pulse in the train. In the acute physiological experiments on the behaviorally trained deaf cats, the average maximum frequency at which significant phase-locking occurred was in each case 100 pps ($P < 0.01$; Rayleigh test) (Mardia 1972). In the behavioral study, 14 psychophysical thresholds were obtained in the deaf cats; 10 of these thresholds were estimated using trains of biphasic pulses at pulse rates ≥30 pps (Table 2). The behavioral results presented in
the preceding text have shown that psychophysical thresholds were lower at a pulse rate of 30 pps compared with a pulse rate of 2 pps (Fig. 4B), suggesting that neural activity driven by higher pulse rates confers a threshold advantage. To test this hypothesis, an experiment was conducted to investigate the spike rates of single ICC neurons to trains of biphasic pulses presented at different intensities relative to a neuron's threshold.

The PSTHs in Fig. 8 depict the normalized rate/level responses of an ICC neuron in a neonatally deafened cat (K101) to trains of biphasic pulses (0.2 ms/phase; 20 repetitions) delivered by an intracochlear bipolar electrode at a rate of 30 ± 3 pps and at amplitudes of −1.0 to +5.0 dB relative to the neuron’s threshold (48.0 dB). At stimulus amplitudes that are 1–5 dB above threshold, the neuron responds with a discharge that is synchronized with the pulse rate, and the response is sustained for the duration of the pulse train. The discharge rate increases significantly at 2 dB above threshold and increases again at 5 dB above threshold. In all neurons that responded in a sustained manner, there was a sharp increase in the discharge rate when the stimulus level was 2 or 3 dB above threshold.

In Fig. 9, A–C, the normalized responses (cumulative spikes/
pulse/repetition) for a representative sample of sustained-response ICC neurons (—; \( n = 4 \)) in the same deaf cat are shown as a function of the first 10 pulses delivered at a pulse rate of 30 pps, respectively at 0, +1, and +2 dB relative to a neuron’s threshold. For each neuron at each amplitude, the cumulative number of spikes increases monotonically as a function of pulse number. The cumulative total number of spikes for the sample of neurons is shown by - - -. The slopes of the - - - vary directly with the amplitude of the pulses, i.e., the rate of spike accumulation across pulses is determined by the stimulus intensity relative to a neuron’s threshold. Although it is not surprising that the number and the amplitude of the pulses affect the accumulation of spikes from a sample of neurons, the results shown in Fig. 9, A–C, suggest how the output from the ICC may be integrated spatially across a population of neurons and temporally integrated across several pulses when the auditory nerve array is stimulated with a train of biphasic current pulses. The model depicted in Fig. 9D illustrates this hypothesis and will be described in DISCUSSION.

Comparison of psychophysical, EABR, and neural thresholds with cochlear histopathology

The data summarized in Table 2 include threshold values and the normalized percentage of surviving spiral ganglion cells for each of the deaf cats. Because the anatomic data were drawn from a small sample of feline cases that were grouped on the basis of the kind of electrode (extracochlear vs. intracochlear) and the mode of stimulation (monopolar vs. bipolar), there is confounding of the groups with cell density. Given this circumstance, a qualitative method was selected to compare the threshold results with the anatomic results. Thus the rank orders of groups Re, Ri, Bi, and Bd on several experimental variables are tabulated in Table 3. Each column in the table identifies the rank of the group means from 1 (highest rank) to 4 (lowest rank) on one variable. The ranks in the three columns on the left (behavioral, EABR, and neural minimum Thresholds) and the rank in the fourth column (% survival of spiral ganglion Cells) are similar. In this data set, thresholds and cell density tend to covary.

Despite the qualitative covariation between thresholds and spiral ganglion cell survival in Table 3, the possibility of spurious associations cannot be excluded on the basis of the available data. Two observations can serve to highlight this caveat. Cell densities for the two cats in group Re were 42.7 and 10.6%, although their psychophysical thresholds were nearly identical (difference = 0.4 dB). A similar disparity was obtained in group Bi. For cats K83 and K86, the fractions of surviving spiral ganglion cells were 69.0 and 39.1%; psychophysical thresholds in these animals were 32.2 and 31.9 dB (difference = 0.3 dB), respectively. Thus within groups Re and Bi, an association between the behavioral and anatomic variables was weak or absent. Similar observations apply as well to comparisons between physiological thresholds and spiral ganglion cell density in these animals.

DISCUSSION

Based on direct comparisons of psychophysical, physiological, and anatomic data obtained from the same animals, the results described in the preceding text include information on neural mechanisms that may underlie behavioral responses to perceptually significant stimuli in electrical hearing. The results provide a context for discussion of four important issues in hearing and deafness research: the value of a feline behavioral model for research on cochlear prostheses; the relationships among psychophysical and electrophysiological thresholds for electrical cochlear stimulation; the contribution of spatial-temporal integration by neurons in the auditory nervous system to psychophysical detection; and the relationship of psychophysical and physiological thresholds to cochlear histopathology.

To facilitate comparisons between psychophysical thresholds and physiological variables, each of the deaf cats in this
study was assigned to one of four groups \((\text{Re}, \text{Ri}, \text{Bi}, \text{or} \text{Bd})\) that were identified by a unique combination of conditions. This scheme is essentially an a posteriori method to reduce variability resulting from two key factors that may influence thresholds: the position (extracochlear vs. intracochlear) of electrode contacts relative to the target spiral ganglion neurons and the mode of stimulation (monopolar vs. bipolar). Implicit in this scheme are the assumptions that at equivalent current levels the potential gradient and current path are different for stimulation with extracochlear and intracochlear electrodes; the spread of current is greater for monopolar compared with bipolar intracochlear stimulation; and localized stimulation of neurons and current shunting may be greater for stimulation with closely spaced bipolar electrodes compared with monopolar electrodes (Finley et al. 1990; Hartmann et al. 1984; Merzenich and White 1977; Pfingst 1990a; Shannon 1985; Shepherd and Javel 1997; Shepherd et al. 1993; Smith and Finley 1997; van den Honert and Stypulkowski 1987).

**Evaluation of the feline behavioral model**

The behavioral model we have developed allows us to investigate the effects of perceptually significant electrical stimulation of the cochlea on the central auditory system. If the
model provides a valid and reliable approach for investigations of neural mechanisms in electrical hearing, then it should generate behavioral data that are consistent with psychophysical results reported by other investigators. In fact the behavioral results described in this report indicate that the model is an appropriate choice for training and testing young, deaf cats and that all basic psychophysical findings are consistent with the extant literature.

An excellent degree of stimulus control over performance was achieved in this study. The FA rates during threshold testing sessions compare favorably with FA rates reported for normal hearing, adult cats tested in a CAR paradigm (Heffner and Heffner 1985), indicating that the deaf cats were attending and reacting to the applied electrical signals. Furthermore, psychophysical thresholds usually were stable over the period of time required for behavioral testing. Detection thresholds estimated with short phase duration electrical pulses in monkeys were likewise reported to be relatively stable over time (Pfingst 1990b).

If electrical stimulation of the cochlea is matched for pulse duration and frequency, electrode placement, stimulus waveform, and stimulus configuration, the range of detection thresholds may still be as large as 20–30 dB across subjects (Pfingst 1990a). Across all animals and conditions in the present study, the difference between the lowest and highest detection thresholds for biphasic pulses (0.2 ms/phase) was 18 dB. When expressed as levels of electrical current, this range is within the range of absolute detection thresholds for short phase duration pulses reported for humans (Moon et al. 1993), monkeys (Pfingst 1988, 1990a), and cats (Smith and Finley 1997; Smith et al. 1995). In the four groups of cats, the largest range of thresholds was 5.2 dB for the cats in group Bi. This value is nearly identical to the threshold difference (3–5 dB) in human subjects reported by Shannon (1985, 1989) for biphasic pulses (0.2 ms/phase; 10–100 pps).

We have shown that increasing the pulse rate of biphasic pulses from 2 to 30 pps produced a significant decrease in detection thresholds. This result is entirely consistent with data for short phase duration pulses reported by other investigators. Thresholds typically decrease on the order of 2–3 dB as a function of increasing pulse rates over a range of 2–200 pps in implanted monkeys (Pfingst and Morris 1993; Pfingst et al. 1979) and humans (Moon et al. 1993; Pfingst et al. 1996; Shannon 1985).

Finally, MRTs varied inversely with the amplitude of the pulses used in the present study. This result and the characteristic shape of the latency-intensity functions are consistent with RT data obtained using acoustic or electrical stimuli in monkeys (Pfingst et al. 1979; Stebbins 1966).

One of the central challenges in integrative neuroscience is to understand the relationship between psychophysical and neural thresholds (cf. Parker and Newsome 1998 for review). Because detection decisions and neural activity are probabilistic, in the current study psychophysical thresholds and neural thresholds in the ICC and the A1 were given statistical definitions (cf. METHODS). We assumed that psychophysical detection thresholds and neural thresholds would be correlated because both kinds of threshold are based on antecedent neural activity generated by electrical cochlear stimulation of the auditory nerve. Given that human subjects can detect a tactile stimulus that generates a single action potential on a single cutaneous peripheral nerve fiber (Valbo and Johansson 1976), this assumption seems reasonable.

Of course thresholds are defined arbitrarily, and if different criteria had been used in the current study to define thresholds, the correspondence between psychophysical and neuronal thresholds may have been altered. For example, a criterion neural response defined in terms of a synchronous discharge rate (cf. Fig. 8) might increase the neuronal threshold by $\geq 1$ dB. However, this definition of threshold would not significantly alter the strong associations observed between behavioral and neural thresholds. A similar argument can be made with respect to comparisons between psychophysical and EABR thresholds. Changes in the criteria used for threshold estimation might change the threshold values, but because both kinds of threshold are based on antecedent neural activity in spiral ganglion cells, it is unlikely that the robust relationship between the two kinds of threshold (cf. Fig. 5B) would be altered significantly by a simple change in the definition of thresholds.

**Comparisons of psychophysical and minimum neural response thresholds.** Direct comparisons of behavioral thresholds and single or multineuronal response thresholds in the same animals have been reported previously from this laboratory (Beitel et al. 1993, 1995, 2000). The results of the present study extend the preliminary results of these reports and indicate that when such comparisons are made, psychophysical detection thresholds and central auditory neural thresholds are closely related. This finding may be contrasted with the very large discrepancies between detection thresholds and auditory nerve thresholds that have been reported for indirect comparisons between species (Pfingst 1988, 1990a).

**Intracochlear bipolar stimulation.** In spite of individual differences in behavioral thresholds and nerve survival, mean psychophysical detection thresholds were virtually identical to averaged minimum neurophysiological thresholds in the ICC and the A1 for radial bipolar stimulation with biphasic current pulses (0.2 ms/phase) in three cats implanted with scala tympani prostheses. Although this result and the results reported previously (Beitel et al. 1993, 1995, 2000) do not prove that ICC and A1 neurons are necessary for detection of perceptually significant electrical stimuli, they provide the first direct evidence that activation of single neurons in the central auditory system may contribute to psychophysical detection of electrical stimuli applied to the deaf cochlea.

As we noted in INTRODUCTION, several investigators have compared psychophysical detection thresholds (measured in}

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**Table 3. Qualitative summary**

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macaque monkeys and humans) and auditory nerve fiber thresholds (measured in cats or squirrel monkeys) and have reported that nerve fiber thresholds are typically higher than behavioral thresholds in these inter-species comparisons (Moon et al. 1993; Parkins and Colombo 1987; Pfingst 1988, 1990a; Pfingst et al. 1991; Shannon 1989). At the behavioral threshold level, however, we assume that the pulsatile stimuli used in the present study were sufficient to activate correspondingly low-threshold neurons at stations in the auditory system from the auditory nerve to the primary auditory cortex. Consistent with this assumption, Hartmann and colleagues measured auditory nerve fiber thresholds in cats using 0.2-ms/phase biphasic current pulses and reported single neuronal thresholds from the auditory nerve to the primary auditory cortex. Consistently low-threshold neurons at stations in the auditory system behaviorally thresholds in these inter-species comparisons reported that nerve fiber thresholds are typically higher than thresholds (measured in cats or squirrel monkeys) and have macaque monkeys and humans) and auditory nerve fiber thresholds can be driven by short phase duration pulsatile stimuli at levels corresponding to detection threshold levels in the cat.

**Monopolar round window stimulation.** For 10 comparisons in four cats implanted with monopolar round window electrodes, minimum neurophysiological thresholds in the ICC and the A1 were higher in each case than psychophysical thresholds—although in two comparisons the difference was <5.5 dB. There is nothing remarkable about the values of the psychophysical or the EABR thresholds shown in Table 2 for the cats in either groups Re or Ri. Rather, the minimum neurophysiological thresholds tend to be high, especially in group Re, which had the three highest neural thresholds recorded in this study.

What are the conditions or factors that may have contributed to the high neural thresholds obtained in the cats implanted with monopolar round window electrodes? One possibility is that neural thresholds were elevated by the surgical or anesthetic procedures required for the recording experiments or by a generalized deterioration of the animals. However, elevated thresholds can be excluded as a factor for the following reason. After recording neural responses evoked by stimulation with the chronically implanted round window electrode, the electrode was removed and a bipolar feline prosthesis was implanted acutely in the scala tympani (Leake et al. 1995). Physiological recording was then resumed, and samples of normal, low-threshold neurons and multineuronal clusters were recorded in the ICC and the A1 of each cat.

The failure to record low threshold neurons in groups Re and Ri may be a consequence of undersampling that population of neurons. Because the total number of ICC and A1 neural thresholds recorded in the four cats in groups Re and Ri (n = 446) was larger than the total number of neural thresholds recorded in the four cats in groups Bi and Bd (n = 418), experimental sampling bias actually favored detection of low-threshold neurons in groups Re and Ri. Overall, however, the samples of recorded thresholds were small; thus inadequate sample size is a factor that may have contributed to recording only relatively high-threshold neurons in groups Re and Ri.

A third factor is the possibility that spread of current during monopolar electrical cochlear stimulation, especially extracochlear round window stimulation, stimulated nonauditory structures. If this occurs, a deaf animal might use nonauditory cues to detect an applied electrical current that spreads outside the cochlea. Hartmann and colleagues (Hartmann et al. 1984) have reported that in cats receiving extracochlear round window stimulation, muscle twitching occurs only at high stimulus intensities (>1 mA). A similar result was described in methods: EMG activity accompanied by twitching movements of the facial muscles occurred only at stimulus levels that were much higher (>8–15 dB) than psychophysical threshold levels, suggesting that extracochlear activation of overt motor responses with associated somatosensory cues were not produced at the levels of electrical stimulation used to estimate behavioral thresholds.

Finally, vestibular afferent fibers in the cat also may be activated by electrical round window stimulation at stimulus intensities that are lower than those required to excite auditory fibers (Hartmann et al. 1984; van den Honert and Stypulkowski 1986). Although a vestibular component may be observed in the EABR, vestibular neural responses apparently do not elicit vestibular sensations in humans (van den Honert and Stypulkowski 1986). Nonetheless, we cannot exclude the possibility that motor (facial) or vestibular neurons were activated by monopolar electrical stimulation in the cats in groups Re and Ri, although behavioral or EABR responses consistent with this possibility were never observed in our subjects.

**Comparisons of psychophysical and EABR thresholds.** Previously published reports have shown that EABR thresholds and behavioral thresholds for electrical stimulation of the cochlea are correlated when measured in the same human subjects (Abbas and Brown 1991) or the same cats (Smith et al. 1994). In the present study, psychophysical and EABR thresholds within each group of cats were clustered at similar stimulus levels, and across the four groups, psychophysical and EABR thresholds were significantly correlated. EABR thresholds were higher than psychophysical thresholds in each of the cats (mean difference = 6.5 dB), although within each cat, the mode of stimulation, the placement and type of implanted electrode, the duration of deafness, and degenerative changes in the spiral ganglion (Leake et al. 1991) and the cochlear nucleus (Hultcrantz et al. 1991; Lustig et al. 1994) were eliminated as potential sources of variability.

Compared with the behavioral detection thresholds, the relatively high EABR thresholds suggest that our method for estimating EABR threshold did not provide a sensitive threshold measure for the low-threshold neurons that presumably are located in the brain stem and the auditory nerve. EABR thresholds estimates are affected by subjective versus objective methods of measurement and by procedural variables, including recording bandwidth, signal sample size, signal/noise ratios, and neural temporal synchronization (Elberling and Don 1987; van den Honert and Stypulkowski 1986). In the present study, a visual detection procedure was used, and the number of signals (n = 500) averaged for estimation of EABR thresholds was perhaps too few to yield a visually identifiable evoked response at lower stimulus intensities, i.e., EABR thresholds may have been systematically overestimated.

**Spatial-temporal integration.**

We assume that auditory detection of electrical cochlear stimulation occurs in a deaf cat when central auditory neurons are activated at or below the animal’s psychophysical detection
threshold. To estimate neural thresholds in this study, biphasic current pulses were applied to the cochlea at a rate of 2 pps, and the minimum amplitude stimuli that evoked neural responses defined the ICC and the A1 minimum neural thresholds in each cat. However, most of the psychophysical thresholds included in this study were estimated using pulse rates ≥30 pps. As shown in the preceding text, psychophysical thresholds were significantly dependent on pulse rate, and RTs were shorter at a pulse rate of 30 pps compared with a pulse rate of 2 pps. These behavioral results suggest that the neural activity evoked by a 30-pps train of pulses may contribute to detection by a deaf cat at stimulus intensities that are lower than those used to define minimum neural threshold.

Several researchers have hypothesized that spatial integration (e.g., integration across nerve fibers) and temporal integration of information by populations of peripheral or central auditory neurons contribute to psychophysical detection in electrical hearing (Donaldson et al. 1997; Parkins and Colombo 1987; Pfingst 1990a; Shannon 1985, 1989; White 1984). A stochastic, neural-perceptual model has been described recently that includes a component for spatial and temporal integration of auditory nerve fiber activity and a behavioral threshold component for single electrical pulses (Bruce et al. 1999; White 1987). In this model, a central detector or comparator integrates spikes from one or more nerve fibers within an integration time window. Behavioral detection threshold is reached when the spike count exceeds a threshold level of spikes. Because psychophysical thresholds are typically lower for trains of pulses (Donaldson et al. 1997; Eddington et al. 1978; Pfingst et al. 1991, 1996; Shannon 1985), neural spatial-temporal integration presumably occurs also over some number of stimulus pulses that fall within the integration time window (200–300 ms) for psychophysical temporal integration. To accommodate stimuli with multiple pulses, the model can be adapted to include the aggregate neural response to a pulse train that occurs within the integration time window of the central detector (M. W. White, personal communication).

We have shown that in the ICC the cumulative number of spikes for a sample of neurons increases monotonically as a function of pulse number, with the rate of increase dependent on the amplitude of the pulses (Fig. 9, A–C). These results may be interpreted as representing an integrated spatial-temporal response in which the output from the ICC, and presumably the input to the ICC, is integrated spatially across neurons and temporally integrated across pulses when the auditory nerve array is stimulated with a train of short-duration biphasic current pulses.

This hypothesis and its putative relationship to psychophysical threshold is illustrated in Fig. 9D by a simple descriptive model, suggested by the spike counting model described above (Bruce et al. 1999; White 1987). The bold dashed line in the diagram represents an arbitrary number of spikes required within an integration time window (200 ms) for psychophysical detection. We assume in this example that an ensemble of ICC neurons is activated by biphasic pulses at a stimulus level that is 2 dB below psychophysical threshold. Responses (total cumulative spikes) of the neurons at their threshold (0 dB, triangle symbols), at 1 dB (+1 dB, round symbols), and at 2 dB (+2 dB, square symbols) above their thresholds are plotted as functions of pulse number (30 pps, lower abscissa) and time after stimulus onset (upper abscissa). When pulse amplitude is 2 dB above the neural threshold (i.e., equivalent to the psychophysical detection threshold), an output from the ICC equal to the total number of spikes required for detection is reached after one pulse by spatial integration across the ensemble of neurons (filled symbol at Pulse 1). When pulse amplitude is only 1 dB above the neural threshold (i.e., 1 dB below the psychophysical detection threshold), four pulses are required to accumulate the same number of spikes (filled symbol at Pulse 4). In this case, temporal integration across pulses and spatial integration across neurons contribute to the aggregate level of neural activity necessary for psychophysical detection. However, at the neural threshold (0 dB), the cumulative response fails to produce the number of spikes required for psychophysical detection.

The model predicts the following results, each of which is consistent with the results obtained in the psychophysical experiments described in the preceding text: 1) Because the interpulse interval for 2 pps (500 ms) exceeds the duration of the temporal integration window (200 ms), psychophysical detection thresholds at this pulse rate are dependent on neural spatial integration. Psychophysical thresholds at 30 pps are lower than psychophysical and minimum neural thresholds at 2 pps (Figs. 4B and 6D) because neural spatial-temporal integration occurs at pulse amplitudes that remain subthreshold at 2 pps. 2) As stimulus intensity increases, spatial integration increases by recruitment of previously unstimulated neurons. RTs are faster at higher stimulus intensities (Figs. 2B and 4C) as a consequence of spatial (2 pps) or spatial-temporal (30 pps) integration of spikes. 3) At equal stimulus intensities, MRTs are faster at 30 than 2 pps (Fig. 4D) because the number of spikes accumulated within the temporal integration window is larger at 30 pps.

Note that our descriptive model is compatible with sampling processes that have been proposed to account for psychophysical temporal integration (cf. Viemeister and Wakefield 1991 for review). For a train of pulses, statistical sampling or multiple short time-constant “looks” at the centrally processed input may occur, for example, during a 200-ms integration interval. An increase in the pulse rate would increase the probability that the cumulative spike count would exceed threshold during one or more “looks,” resulting in improved detection performance (a lower threshold).

We have indicated in the preceding text that the physiological results reported in this study do not prove that ICC or A1 neurons are necessary for detection of perceptually significant electrical stimuli, although these results provide direct evidence that activation of single neurons in the central auditory system may contribute to psychophysical detection of electrical stimuli applied to the deaf cochlea. The model illustrated in Fig. 9D was derived with reference to data obtained from ICC neurons. However, spatial and spatial-temporal integrations of neural activity occurring at levels of the auditory system, from the auditory nerve to the primary auditory cortex, are probably essential for psychophysical detection in electrical hearing.

**Relationship of psychophysical and physiological thresholds to cochlear histopathology**

The number of animals included in psychophysical studies of electrical hearing is typically small, whereas the number of variables that contribute to the observed effects of electrical
cochlear stimulation is invariably large. The inevitable consequence is potentially confounded variables. In the present study, cell density was confounded with animal group variables (electrode type and stimulation mode), and the analysis of the relationship between cochlear histopathology and thresholds was limited, therefore to qualitative comparisons. Because variability was large in two groups of cats that received similar treatments, we conclude that the results of this study provide little or no support for the notion that behavioral and physiological thresholds for electrical cochlear stimulation are correlated with ganglion cell density. However, this conclusion must be qualified. Groups Re and Ri were implanted with round window electrodes, and to allow comparison with the cats implanted with intracochlear bipolar electrodes (groups Bi and Bd), cell density was measured in all of the cats as percent of normal for all cochlear regions in the stimulated ear. Any relationship between thresholds and nerve survival in sectors of the cochlea adjacent to intracochlear stimulating electrodes would be obscured by the measure of cell density used in the current study.

The history of attempts to correlate the histopathological status of the cochlea with behavioral and electrophysiological thresholds is ambiguous at best. Studies in monkeys have shown that a qualitative, approximately inverse relationship exists between nerve survival and psychophysical thresholds when measured in the same animals (Pfingst et al. 1981), although the putative relationship (fewer neurons, higher thresholds) is especially weak for short phase duration stimuli (Pfingst and Sutton 1983). Furthermore, better intensity discrimination in monkeys was associated with poorer nerve survival (Pfingst et al. 1983).

In electrophysiological studies, Wave I amplitude of the EABR has been correlated with spiral ganglion cell population size (Hall 1990), but EABR measures generally have not been successful as predictors of ganglion cell survival. Several investigators have shown poor correlations between the later waves of the EABR (Waves II–IV) and the number of surviving spiral ganglion cells in cats and rats (Hall 1990; Shepherd and Javel 1997; Shepherd et al. 1983), although Hall (1990) also has shown that the Wave III negative peak to Wave IV positive peak amplitude (N3-P4) may be positively correlated with ganglion cell survival in the rat.

**Factors contributing to variability in spiral ganglion cell density**

The anatomic data in the present study were obtained from cats with idiosyncratic histories of deafness and chronic electrical cochlear stimulation (cf. Table 1). Variability in cell density in these animals may be attributed at least partially to two factors that are known to affect the survival of spiral ganglion cells: the duration of deafness and the protective effect conferred by chronic electrical stimulation of the cochlea.

**Duration of deafness.** Spiral ganglion cell survival was especially variable within groups Re and Bi (cf. Table 2). For the two cats in group Re, the duration of deafness (cf. Table 1) was >52 wk (CH332) versus 34 wk (K90); the fraction of surviving spiral ganglion cells in these animals was 10.6 versus 42.7%, respectively. In group Bi, the cat with the longest duration of deafness (K86, 55 wk) had the poorest neural survival (39.1%), and the cat with the shortest duration of deafness (K83, 32 wk) had the largest fraction of surviving cells (69.0%). The cats in groups Ri and Bd had similar durations of deafness and similar fractions of surviving cells. It is known that cell survival is a function of the duration of deafness (Leake and Hradek 1988), and this effect may account partially for the variable cell survival seen within groups Re and Bi.

**Protective effects of chronic electrical stimulation.**

Anatomic studies comparing the stimulated and unstimulated cochleae in deafened animals have revealed that chronic intracochlear electrical stimulation delays or partially prevents the atrophy of spiral ganglion cells in the stimulated cochlea (Hartshorn et al. 1991; Leake et al. 1991, 1995, 1999; Lousteau 1987). The protective effects of chronic electrical stimulation may have contributed to variability in cell survival between the different groups of animals in the present study. In group Re, one cat was not stimulated chronically (CH332), and chronic extracochlear stimulation had no effect on the pattern of cell survival in the stimulated cochlea of the second cat (K90) (Leake et al. 1995). The two cats in group Bd (K93 and K94) received chronic intracochlear stimulation. However, stimulation-induced damage to the cochlea and spiral ganglion neurons during EABR sessions with a defective stimulator may have offset any protective effects in these cats.

The cats in group Bi (K83, K84, K85, and K86) received chronic intracochlear bipolar stimulation, and the cats in group Ri (K80 and K82) received chronic extracochlear bipolar stimulation. Each of the cats in these two groups showed a protective effect of chronic intracochlear electrical stimulation (Leake et al. 1995, 1999), and the five largest proportions of surviving spiral ganglion cells were obtained from morphometric analyses of the stimulated cochleae in these six animals (cf. Table 2).

**Chronic electrical cochlear stimulation**

The spatial and temporal representations of electrical signals in the inferior colliculus are modified by chronically applied electrical cochlear stimulation in neonatally deafened cats (Snyder et al. 1990, 1991, 1995; Vollmer et al. 1999). Although the kittens received chronic stimulation in the current study, the observed psychophysical and neural thresholds were probably not affected by this experimental procedure. This conclusion is based on evidence described in the preceding text suggesting that behavioral and EABR thresholds were essentially stable for the periods of time required for threshold estimations. Furthermore, research in our laboratory has shown that mean response thresholds for sinusoidal stimulation (100 Hz) (Snyder et al. 1990, 1991) and pulsatile stimulation (0.2 ms/phase) (unpublished data) are equivalent for ICC neurons in two groups of cats: adult deafened, unstimulated cats and neonatally deafened, chronically stimulated cats. Chronically stimulated sectors of the cochlea may acquire an expanded representation in the ICC that includes a larger number of neurons that are activated by projections from those sectors of the cochlea, but the available evidence suggests that psychophysical and neural thresholds for short phase duration pulses are not affected by chronic electrical cochlear stimulation.
Future directions

The results of this study have shown that psychophysical thresholds were influenced by pulse rate, suggesting that spatial-temporal integration in the central auditory system contributes to detection of electrical pulses applied to the cochlea. Additional behavioral and neurophysiological research is required to determine whether stimulus-induced alterations in the central auditory system enhance or diminish signal processing capacity and behavioral performance and whether the alterations are dependent on specific parametric characteristics of the applied electrical stimuli. Research along these lines will generate basic information on the spatial representation and the temporal encoding of electrical signals in the central auditory system that eventually may be incorporated in signal processing strategies and cochlear implant designs to provide the most appropriate conditions for electrical hearing in profoundly deaf individuals.

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