Neuronal Responses in Cat Primary Auditory Cortex to Electrical Cochlear Stimulation. III. Activation Patterns in Short- and Long-Term Deafness

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Raggio, Marcia W. and Christoph E. Schreiner. Neuronal responses in cat primary auditory cortex to electrical cochlear stimulation. III. Activation patterns in short- and long-term deafness. J. Neurophysiol. 82: 3506–3526, 1999. The effects of auditory deprivation on the spatial distribution of cortical response thresholds to electrical stimulation of the adult cat cochlea were evaluated. Threshold distributions for single- and multiple-unit responses from the middle cortical layers were obtained on the ectosylvian gyrus in three groups of animals: adult, acutely implanted animals (“acute group”); adult animals, 2 wk after deafening and implantation (“short-term group”); adult, neonatally deafened animals (“long-term group”) implanted after 2–5 years of deafness. For all three groups, we observed similar patterns of circumscribed regions of low response thresholds in the region of primary auditory cortex (AI). A dorsal and a ventral region of low response thresholds were found separated by a narrow, anterior-posterior strip of elevated thresholds. The two low-threshold regions in the acute and the short-term group were arranged cochleotopically. This was reflected in a systematic shift of the cortical locations with minimum thresholds as a function of cochlear position of the radial and monopolar stimulation electrodes. By contrast, the long-term deafened animals maintained only weak or no signs of cochleotopy. In some cases of this group, significant deviations from a simple tri-partition of the dorsoventral axis of AI was observed. Analysis of the spatial extent of the low-threshold regions revealed that the activated area in acute cases was significantly smaller than the long- and short-term cases for both dorsal and ventral AI. There were no significant differences in the rostrocaudal extent of activation between long- and short-term deafening, although the total activated area in the short-term cases was larger than in long-term deafened animals. The width of the narrow high-threshold ridge that separated the dorsal and ventral low-threshold regions was the widest for the acute cases and the narrowest for the short-term deafened animals. The findings of relative large differences in cortical response distributions between the acute and short-term animals suggest that the effects observed in long-term deafened animals are not solely a consequence of loss of peripheral innervation density. The effects may reflect electrode-specific effects or reorganization changes based on factors such as differences in excitatory and inhibitory balance.

INTRODUCTION

Use of cochlear implants for the treatment of deafness has revealed significant improvements for auditory capabilities for both pediatric and adult recipients. Some patients only gain improved lip-reading ability or environmental sound awareness, whereas others experience significant increases in speech understanding (Hollow et al. 1995; Skinner et al. 1997; Tyler et al. 1997). Implanted children demonstrate differing levels of auditory ability depending on a number of factors, including age at onset of deafness, duration of deafness, age at implantation, length of time implanted, speech-processing strategy, educational environment, degree of aural/oral habilitative training, and family support (Cowan et al. 1995; Miyamoto et al. 1994; Osberger et al. 1998; Snik et al. 1997; Tyler et al. 1997; Waltzman 1997). Duration of deafness, age at implantation, and duration of implant use also play a major role in adult implant performance (Blamey et al. 1996; Dawson et al. 1992). The percentage of adults and children who enjoy considerable open speech understanding appears to be growing with improvements in the number of sound-processing channels and speech-processing algorithms (Brill et al. 1997; Dorman and Loizou 1998; Hollow et al. 1995; Whitford et al. 1995; Wilson et al. 1991; Zimmerman-Phillips et al. 1997). Adults with congenital deafness, however, do not appear to make significant progress in this area, although congenitally and perilingually deafened pediatric implantees perform progressively better, in terms of speech reception and production, the longer they are implanted and stimulated (Manrique et al. 1995; Tyler et al. 1997; Waltzman 1997; Zimmerman-Phillips et al. 1997; Zwolan et al. 1996).

These observations suggest that several factors contribute to patient performance including length of sound deprivation, stimulation history, cognitive learning abilities, and capacity for auditory plasticity. The effects of auditory deprivation, particularly profound deafness, on the auditory system have demonstrated clear changes in the central auditory pathway, including spiral ganglion cell degeneration, shrinkage of auditory brainstem neurons, reduction in auditory brainstem neuron number, aberrant neural projections, and physiological responses as well as reductions in metabolic activity (Hinojosa et al. 1987; Nadol et al. 1989; Otte et al. 1978; Reuter et al. 1997). An important factor is the age at which deafness occurs (Silverman and Clopton 1977; Webster 1983, 1988). Significant reductions in the number of auditory brainstem neurons has been observed when the loss occurs in early life (Webster and Webster 1977) versus those that occur in adults (Moore 1994; Trune 1982). There is only rudimentary maintenance of the cochleotopic organization of primary auditory cortex (AI) after congenital deafness (Shepherd et al. 1997). Therefore, although it seems clear that variations in speech understanding can be attributed to issues surrounding electrode design, speech...
coding strategies, and stimulus characteristics, it appears that anatomic limitations, and subsequent physiological alterations in central auditory nervous system processing capacities, also can be responsible for patient performance (Ponton et al. 1996; Shepherd et al. 1997).

To begin to understand the effects of auditory deprivation on performance and the efficacy of electrical stimulation on the organization or reorganization of the auditory system, it is essential to evaluate the physiology of the central auditory system in animals deafened for different lengths of time and using various electrical stimulation strategies. Two main issues must be addressed: what is the effect of age of deafness onset and duration on the functional organization of central auditory stations and how does chronic, patterned, electrical stimulation effect that organization. We have begun to explore these issues in an animal model at the level of AI. Fundamental to the answer to these questions is an appreciation of the basic yet systematic, physiological properties of AI. A number of acoustical studies have been conducted in cat AI that revealed several physiological properties with distinct spatial distributions. Microelectrode studies of spectral distributions in cat AI neurons (Merzenich et al. 1975; Reale and Imig 1980) have revealed an orderly representation of characteristic frequency across the rostrocaudal dimension of AI and a variation in spectral selectivity and sensitivity along the dorsoventral dimension of AI (Heil et al. 1992; Mendelson et al. 1997; Schreiner and Mendelson 1990; Schreiner and Sutter 1992; Schreiner et al. 1992).

These distributions demonstrate that physiological responses in primary auditory cortex, using acoustic stimulation, offer a systematic functional framework against which the central representation of peripheral electrical stimulation can be compared. For that reason, as well as the fact that reorganizational capacities may be more strongly expressed at the cortical level relative to the subcortical stations, AI was chosen as an appropriate central auditory site to measure the responses of neurons to multielectrode cochlear implant stimulation.

The current study was undertaken as an initial effort to evaluate the questions: 1) how are responses from cochlear implant stimulation spatially represented in AI? 2) How are these representations affected by acute implantation with possible, partial hair cell survival and complete spiral ganglion cell survival? 3) How are these representations affected by short-term deafening and complete spiral ganglion cell survival? And 4) how are these representations affected by long-term neonatal deafening with a high degree of degeneration of spiral ganglion cells?

Some of the most relevant parameters for implants served as independent variables: location of stimulation, spatial pattern of stimulation (monopolar, bipolar, radial, longitudinal), and duration and onset of deafness. Dependent variables include: sensitivity to electrical stimulation (response threshold) and spatial distribution of response sensitivity across primary auditory cortex.

METHODS

Most technical details of this study have been described in some detail in previous reports from this series of studies (Raggio and Schreiner 1994; Schreiner and Raggio 1996) and therefore will be summarized only briefly.

Neuronal responses in the auditory cortex evoked by electrical stimulation of the cochlea were recorded from the right hemisphere of healthy, adult cats (Felis catus) after each animal received a left scala tympani cochlear implant. Animals were segregated into three groups according to the duration of deafness. The first group consisted of five adult, neonatally deafened cats that were implanted between 2 wk and 4 mo before the electrophysiological evaluation and studied 33–69 mo after birth (“long-term group”). Two of the five long-term deafened animals (K55 and K56) received chronic electrical stimulation of the cochlear implant for 2–4 mo immediately before the electrophysiological evaluation of cortex. Both animals were stimulated for 2–6 h/day either passively or as part of behavioral detection or discrimination tasks. The two other groups were normal hearing adult cats that were either implanted acutely (“acute group,” n = 7) or deafened and implanted 2 wk before study (“short-term group,” n = 5).

Deafening procedures

Before implantation of the intracochlear electrode and recording from cortical cells, the animals were deafened using one of three procedures. For the long-term group, beginning 24 h after birth, intramuscular injections of neomycin sulfate were administered for 16–21 days at 50 mg·kg⁻¹·d⁻¹ (Snyder et al. 1990). For the acute group, monaural hearing loss was induced by insertion of the stimulation electrode into the scala tympani (n = 6) or by intrascalar injection of neomycin sulfate (50 mg/ml) followed by electrode insertion (n = 1) several hours before recording from auditory cortex. In animals deafened by electrode insertion, an electrically evoked auditory brain stem response (EABR) was measured several hours after insertion. The EABR was not tracked over time because earlier studies (Hartmann et al. 1984; Snyder et al. 1990) have suggested that there is little difference in the physiological behavior, EABR thresholds, and waveform of responses in inferior colliculus neurons between acutely deafened and implanted animals and animals that had not been deafened, but acutely implanted. For the short-term group, bilateral deafening was induced by a single subcutaneous injection of kanamycin (400 mg/kg) followed by a subcutaneous injection of aminooxyacetic acid (AOAA) (25 mg/kg) (Leake et al. 1987) or slow iv administration of ethacrynic acid (10–25 mg/kg) (Xu et al. 1993).

Implantation and surgery

Animals of the acute group underwent cochlear implantation under nonsterile conditions several hours before recording from cortical neurons. Animals from the short- and long-term group were implanted under sterile conditions ≥2 wk before the electrophysiological mapping experiment. Animals were sedated with an intramuscular injection of a 4:1 mixture of ketamine hydrochloride (10 mg/kg) and acepromazine maleate (0.10 mg/kg). After venous cannulation, an initial dose of pentobarbital sodium (15–30 mg/kg iv) was administered. Anesthesia was maintained at areflexic levels with supplementary intravenous injections of pentobarbital sodium and during experimental procedures with a continuous infusion of pentobarbital sodium (2 mg·kg⁻¹·h⁻¹) in lactated Ringer solution (infusion volume ~3.5 ml/h). The animals also were administered dexamethasone sodium phosphate (0.14 mg/kg), atropine sulfate (0.04 mg/kg im), and prophylactic antibiotic treatment (Penicillin G100K units). A tracheotomy was performed and a tracheal tube placed to ease breathing. The body temperature of the animals was maintained at 37.5°C by means of a heated water blanket with feedback control. An elliptical incision was made through the scalp and a posterior temporalsis muscle flap created. The bulla then was exposed and opened, thereby exposing the round window. The round window membrane was opened and the intracochlear electrode inserted into the scala tympani. Once in place, the silastic electrode carrier was secured to the promontory and under the temporalsis flap using a butyl cyanoacrylate adhesive (Histocryl).

The animal’s head was mounted in a standard mouth-bar head holder. The temporalsis muscle was then retracted and the right lateral
cortex was exposed. Because the area of the basilar membrane subtended by the scala tympani electrode was restricted to the most basal 8 mm, only the presumed central and rostral-most sectors of primary auditory cortex were exposed and mapped. The exposed cortical region was covered with silicone oil and a video image of the surface vasculature obtained. Electrode penetration sites were marked on a video picture of the cortical surface.

**Stimulus generation and presentation**

Electrical pulse stimuli were generated and controlled by a signal processing computer (TMS32010) and converted to an analogue signal by a 16 bit D/A converter running at a 60-kHz sampling rate. A low impedance attenuator was used to control electrical current in a range from 1 μA to 30 mA (Vureck et al. 1981). Stimuli then were delivered to an electrode pair switch box connected by cable to the electrode connector at the animal’s head. Electrical stimuli consisted of capacitively coupled, charge balanced, biphasic square wave pulses of 200 μs/phase, delivered at 1–2 pps and with an interstimulus interval of 500–1,000 ms. Electrical current levels are expressed in dB re 100 μA.

**Recording procedure**

Experiments were conducted in a double-walled, sound-shielded room (IAC). Parylene-coated tungsten microelectrodes (Microprobe) with impedances of −0.8–1.2 MΩ at 1 kHz were introduced into the auditory cortex with a hydraulic microdrive (KOPF) remotely controlled by a stepping motor. All penetrations were essentially orthogonal to the brain surface. The recordings reported here were obtained at intracortical depths ranging from 850 to 1,050 μm, as determined by the microdrive setting after correction for “dimpling” of cortical surface. (That is, when significant dimpling was observed with electrode insertion, the electrode was advanced ~600 μm deeper and then withdrawn until the cortical surface was again flat, before the depth was accepted as truly within the intended 850–1,050-μm range). Activity of small clusters of neurons or single neurons was amplified, band-pass filtered, and monitored on an oscilloscope and an audio monitor. Spike activity was isolated from the background noise with a window discriminator (DIS-1, Microprobe). Threshold mapping was the singular goal of electrical stimulation in this portion of the study. Audiovisual criteria of minimum driven spike activity from single units or small cluster of units were used in most cases to determine the minimum threshold values for a current range of 30–3,000 μA. A single measure of threshold determination was made at each penetration site using an ascending/bracketing method for each electrode configuration. In this series, several radially and longitudinally configured bipolar electrode pairs were stimulated as well as several monopolar conditions with the reference electrode placed at the neck of the animal. Several designs of scala-tympani electrodes were used, resulting in various spacings of the bipolar pairs and locations of the individual electrode contacts. Because only a few actual stimulation electrode positions could be obtained at the conclusion of the experiment, estimates of the positioning of the electrodes was obtained relative to the electrode cuff at the round window and the distance of the electrode contacts from the cuff.

**Statistical analyses**

Statistical analyses of the data were performed using Statview (Abacus Concepts). The following analyses were performed if appropriate: factorial ANOVA for condition differences; Pearson linear regression analysis for intraparametric relationships; and principal component analysis for multivariant analysis. Generally, only statistically secure results with P < 0.05 are reported.

**Data representation**

One method of data representation throughout these studies is the use of two- and three-dimensional reconstructions that represent the spatial distributions of parametric responses across the primary auditory cortical surface (see Fig. 1). These reconstructions were performed with a software package (Surfer Golden Software) using standard methods for pseudo-three-dimensional representation applied in geological studies to represent terrain. The methods are based on an interpolation algorithm that weights the values of the two nearest neighboring points in each quadrant according to an inverse square distance law and calculates the values necessary for a complete description of the mapped area. For each recording site, the minimum response threshold for a given electrode configuration is noted at the corresponding site in the map. Iso-threshold contours are determined on the basis of the spatial distribution pattern. The actual spatial locations of the recording sites were used to generate a two-dimensional grid of the represented area by projecting the actual sites to the nearest grid point. A third dimension, coloring, corresponds to the averaged local magnitude of a functional parameter at a given site. The color code is quite faithful to the raw data, as demonstrated in a previous paper that used the same algorithm (Mendelson et al. 1997). From the resulting interpolated spatial pattern, three quantitative measures were obtained (see Fig. 1D, dashed lines): 1) the maximal caudalrostral spatial extent of the region near minimum threshold. This width of spatial tuning (STW) was determined 6 dB above minimum threshold. Because in many cases there was a dorsal minimum and a separate, ventral threshold minimum, both STWs were obtained. Usually, there was a single recording location with minimum threshold in either area. However, if there were several locations with equally low thresholds, the location yielding the widest rostral-caudal extent was used as estimate of spatial tuning. 2) The cortical area occupied by locations with thresholds not more than 6 dB above minimum threshold. In Fig. 1D, thick solid lines mark the boundaries of those regions. And 3) the width of the high-threshold ridge (RW) separating dorsal and ventral regions of local threshold minima.

**RESULTS**

In 17 deafened cats, response thresholds to electrical cochlear stimulation were mapped on the ectosylvian gyrus of the right cortical hemisphere. Three groups of animals were studied that differed in the induction method and duration of their hearing loss (see Table 1). Penetration locations were chosen to cover evenly the high-frequency region of AI. We made an effort to keep the spacing of the penetrations between 300 and 600 μm and approximately equal across each map to minimize spatial biases. Because in most of these cases, no physiological measures of the actual location of AI were available, such as the tonotopic gradient (Merzenich et al. 1975) or the location of the sharply tuned region in AI (Schreiner and Mendelson 1990), distinct anatomic features had to serve as main landmarks. In general, the mapping was limited to the region between the anterior and posterior ectosylvian sulci, in the rostrocaudal direction, and between the supra-sylvian sulcus and a line ~2–3 mm ventral to the connection line between the dorsal tips of the anterior and posterior ectosylvian sulci. This line is, in our experience (e.g., Schreiner and Cynader 1984; Schreiner and Mendelson 1990; Schreiner and Sutter 1992), located close to the transition zone between AI and the second auditory field (AII). However, the actual extent of the mapped area depended on several other constraints, including the extent of regions that showed low response thresholds, a continued physiologically viable status of the animal, as well as the specific nature of sulcal and vascular patterns that can render certain regions inaccessible. Accordingly, the number of penetrations and the extent of the mapped area could vary substantially (see Table 1). The mean number of electrode penetrations per animal was 83 ± 30 (mean ± SD; n = 17). There
was no statistically significant difference between the number of penetrations for the three groups of animals; however, the short-term group tended, on average, to have a smaller number (69 ± 30) than the long-term group (104 ± 32) and the acute group (77 ± 25). The mapped area was, on the average, 29.1 ± 15.8 mm². Again, there was no statistically significant difference between the groups, although the acute group tended to have a slightly smaller map size (21.2 ± 8.3 mm²) than the short-term (38.3 ± 4.1 mm²) and long-term groups (32.3 ± 24.5 mm²).

**Pattern of threshold distribution in primary auditory cortex**

For each electrode configuration of the scala-tympani electrode, a distinct spatial pattern of response thresholds across the mapped region was observed. Local regions of low-threshold responses were separated from regions with high-threshold responses or unresponsive areas. First we will provide a qualitative description of the main aspects of the spatial response distributions in AI followed by a quantitative evaluation of several prominent features of these distributions.

Examples of the reconstructed cortical response-threshold distributions for different locations and configurations of the cochlear stimulation electrodes are shown in Figs. 2–6. The response-threshold maps illustrated in Fig. 2 are from an animal that was acutely implanted and mapped immediately. The approximate location of the mapped region on the right ectosylvian gyrus is indicated as the shaded region in a small schematic plot. The threshold distributions are shown for five bipolar electrode configurations with four radial electrode pairs and one longitudinal pair. Each panel shows the interpolated threshold distribution based on 101 recording sites. The actual cortical location of each recording site is shown in the panel for the longitudinal electrode pair 1,8 (black dots). The individual threshold values were transformed onto a color code (bottom right; see METHODS). Iso-threshold contours are shown (solid lines) in increments of 4 dB, starting 4 dB above the lowest threshold value encountered for each electrode pair. Inspection of the different threshold distributions reveals clusters of penetrations with equally high (red to orange) or low (purple to blue) thresholds. Characteristically, along the ventral-dorsal axis of the map one can distinguish two regions of lower thresholds that are separated by a narrow ridge of higher response thresholds. The rostrocaudal location of the ventral and dorsal low-thresholds regions is quite similar and depends on the cochlear location of the stimulation electrode. More basally located electrode pairs (e.g., p7,8) result in more rostrally located subregions of low thresholds than more api-
threshold region, or the spatial tuning, is wider; and stimulation of the longitudinal electrode pair produces a nearly flat threshold profile in the dorsal area, i.e., without hot spots and threshold increments between the location of the individual contacts of the longitudinal electrode pair.

The next example shows four different maps for a short-term deafened case (Fig. 4). Although the main aspects of the maps are similar to those illustrated for the acutely deafened animals, several differences can be noted. Both dorsal and ventral regions of low thresholds appear to have a wider rostrocaudal extent than in the examples for acute deafening. The rostrocaudal location of the dorsal and ventral threshold minima do not appear to be aligned in the same rostrocaudal plane as in the acute cases. There appears to be only a slight, although still discernible, shift of low-threshold locations with radial electrode location. The high-threshold ridge between the dorsal and ventral low-threshold regions is less developed than in the acute examples. The threshold distribution pattern for a monopolar electrode configuration (p1m) is very similar to the corresponding radial pair, although its minimum threshold is ~10 dB lower. The threshold pattern for the longitudinal electrode configuration (p1,4) is also quite similar to the pattern for the monopolar electrode.

Threshold maps for a long-term deafened animal are shown in Fig. 5. Despite 5.67 yr of deafness, the basic threshold patterns for the different electrode configurations are quite similar to those demonstrated for the acutely deafened cases. In particular, there are two focal regions, a dorsal and a ventral, of lower thresholds separated by a horizontal ridge of higher thresholds. However, only slight shifts in minimum threshold location are apparent with change in cochlear stimulation site. The threshold pattern for the monopolar configuration does not differ substantially from those for the corresponding radial electrodes, although the minimum threshold is lower than for radial stimulation. The pattern for the bipolar longitudinal configuration is again quite similar to the two monopolar patterns of its constituent electrodes.

Another example of threshold maps from an acutely deafened and mapped animal is shown in Fig. 3. Similar to the previous case, dorsally and ventrally located circumscribed low-threshold regions can be seen for the radial electrode pairs and a broad low-threshold region for the longitudinal pair. In this case, the ventral region of low thresholds appears smaller perhaps because it falls largely outside the mapped area. For the different radial pairs, a difference in the rostrocaudal location of the dorsal low-threshold region is again discernible. However, several features of the threshold maps are slightly different from the previous case (Fig. 2): the horizontal high-threshold ridge is wider; the rostrocaudal extent of the low-

cally located electrodes (e.g., p1,2). This relationship suggests a maintained cochleotopic organization of AI with electrical cochlear stimulation. Stimulation of the longitudinal electrode pair (Fig. 2; p1,8) results in two rostrocaudally elongated regions of low-medium thresholds. These regions include and are potentially limited by the sites of the most basal and apical radial electrode pairs. In this case, each region of low thresholds has two local minima near the location most responsive to the two individual electrode locations (electrode contacts 1 and 8). In other words, the longitudinal stimulation results in two “hot spots” as suggested by the response location of the radial pairs including those contacts. However, the threshold elevation in between the two contacts of the longitudinal pair is relatively small compared with the highest thresholds encountered in this map. A high-threshold ridge between the dorsal and ventral low-threshold regions is expressed clearly in particular for the longitudinal configuration.

Another example of threshold maps from an acutely deafened case (Fig. 6) reveals that the threshold pattern can differ substantially from the previously illustrated examples. Relatively diffuse and patchy patterns of low- and high-threshold regions can be seen in long-term cases. No clearly separated or circumscribed regions of low threshold are present. Similarly, there is no clear indication of an extended horizontal high-threshold ridge, although there is a central patch of higher thresholds at a dorsoventral position compatible with the usual location of the high-threshold ridge. Overall, the thresholds generally were quite low, despite 2.75 yr of deafness. This animal showed the most idiosyncratic organization of AI of all 17 cases.

In summary, the examples demonstrate some general principles of the spatial organization of AI for the response sensitivity to cochlear electrical stimulation. Two regions of low response thresholds, separated in the dorsoventral domain by a high-threshold ridge, generally appear with electrical cochlear stimulation. However, details of the spatial pattern, such as extent and relative location of regions with low response thresholds, can vary with the specific electrode configuration and with the deafening history of the animals. In the next sections, several specific aspects of the spatial distribution pattern will be analyzed and compared for the different experimental groups.

TABLE 1. Summary of deafening procedure, deafness duration, number of electrode penetrations, and cortical mapping extent

<table>
<thead>
<tr>
<th>Animal</th>
<th>Deafening Procedure</th>
<th>Deafness Duration, mo</th>
<th>No. of Penetrations</th>
<th>Extent of Mapping, mm</th>
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<tr>
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<td>6.4 x 6.6</td>
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<td>Aminoglycoside</td>
<td>69</td>
<td>110</td>
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Electrode configuration effects on cortical response parameters

One of the potentially confounding influences on the results of this study is that several different designs of the scala-tympani electrode were used. This variability in the experimental design was due to advances in electrode technology over the extended time frame of the study (>8 yr) and limited availability of some electrode types. As a consequence, some details of the size and position of the electrode contacts as well as the longitudinal and radial spacing of the bipolar electrode configuration varied between and within experimental groups. Examples of the three main electrode types are demonstrated as schematic drawings in Figs. 2–6. The distribution of the longitudinal spacing of the actually used configurations is shown in Fig. 7 for the three deafness groups. A total of 85 stimulation configurations were used in the 17 animals, with an average of 5 conditions per animal. Fifty of these configurations were bipolar with a longitudinal spacing equal to or <1 mm. These conditions were designated as true radial or offset radial configurations. Fourteen different longitudinal configurations were used, usually defined as the widest spacing between electrode contacts that each resulted in a low-threshold response either as a monopole or as part of a radial configuration. The resulting spacing varied between 2 and 6 mm. Twenty-one monopolar configurations were tested. However, no monopolar stimulation was tested in the acute group.

FIG. 2. Reconstruction of cortical response threshold distributions for different locations of the cochlear stimulation electrodes. Acutely implanted animal C163. The approximate location of the mapped region on the right ectosylvian gyrus is indicated as the shaded region in a small schematic plot (SS, supra-sylvian sulcus; PE, posterior ectosylvian sulcus; AE, anterior ectosylvian sulcus). A schematic drawing of the stimulation electrode shows the position of the individual contacts and their numbering. Spacing of the vertical lines across the schematic electrode corresponds to 1 mm. The most apical electrode pair was located ~43% from cochlear base. The distributions are shown for five bipolar electrode configurations with four radial electrode pairs and one longitudinal pair. Each panel shows the interpolated threshold distribution based on 101 recording sites. Cortical location of each recording site is shown in the panel for the longitudinal electrode pair 1,8 (●). Actual threshold values were transformed onto a color code shown (bottom right). Color-coded threshold range for each electrode configuration is given above the color bar. Iso-threshold contours (—) are shown in increments of 4 dB, starting 4 dB above the lowest threshold value encountered for each electrode pair.
Before analyzing the effects of deafness duration and electrode configurations on various response parameters, we determined whether the differences in spacing of the contacts in the longitudinal electrode configurations interacted with the measured parameters. A correlation analysis between electrode spacing and response parameters was performed that revealed no statistically significant influence of the degree of longitudinal spacing between 2 and 6 mm for any of the parameters. However, there were a number of significant differences between the narrowly spaced “radial” electrode configurations and the more widely spaced “longitudinal” configurations as well as the monopolar configurations. Accordingly, the following data presentation will only distinguish among bipolar radial configuration (1 mm longitudinal spacing); bipolar longitudinal configuration (2–6 mm longitudinal spacing); and monopolar configuration (extracochlear return electrode with >20 mm separation).

Cochlear electrode position effects on location of threshold minima in cortex

Among the main aspects of cortical activation patterns that can be deduced from the example maps (Figs. 2–6) is that the cortical position of the region(s) with lowest response threshold can covary with the position of the stimulation electrode in the cochlea. We tested the hypothesis that cortical activation by electrical cochlear stimulation reflects the same cochleotopic organization of AI as seen in normal, hearing animals. For that purpose, the relative relationship between cochlear position (expressed as distance of basilar membrane in percent from the cochlear base) and rostrocaudal cortical distance (expressed in millimeter) had to be established. This was accomplished by first ascertaining the relationship between cortical characteristic frequency (CF) and relative cortical position. From eight previously obtained CF maps of AI in normal hearing animals (689 recording locations) (e.g., Raggio 1992; Schreiner and Mendelson 1990; Schreiner and Sutter 1992) the CF versus cortical place information was pooled. Only CFs >5 kHz were used, the region relevant for the current study, and the linear regression slope of log(CF) versus cortical distance for the individual cases was normalized to the average slope. Because only relative distances were required for the current analysis, the CF of 6.5 kHz was arbitrarily chosen as origin (0 mm) of the rostrocaudal cortical position, in every case. The resulting cumulative distribution of CF versus cortical location is plotted in Fig. 8. A fit with an exponential regression (—) was highly significant and accounted for 90% of the variance. Combining this relationship with the known relationship between cochlear CF and basilar membrane position (Greenwood 1961), the relationship between cortical distance ($D_{cortex}$ in millimeters) and basilar membrane distance ($D_{cochlea}$ in percent from base) can be approximated as

$$D_{cortex} = -0.127 D_{cochlea} + \text{Constant}$$

The additive constant depends on the reference point. In the following analysis, the cochlear position of 47% was equated with the cortical position zero, resulting in Constant $= 5.97$.

To test whether the relationship between cochlear position of stimulation and cortical response location along the rostrocaudal axis of AI is maintained for electrical stimulation, the cortical position of lowest threshold for focal cochlear stimu-
lation was obtained. The relative cortical positions for both the dorsal and ventral threshold minima were plotted as a function of the electrode position in the cochlea. The location data for the radial bipolar and the monopolar electrode configurations were combined because both showed distinct, spatially confined threshold minima. The cortical positions for different stimulation electrode locations first were plotted separately for each individual case and a regression analysis was performed. The individual regressions were adjusted to align arbitrarily the cochlear position of 47% with the cortical position of 0 mm. After pooling the cases relative to this reference for each of the three experimental groups, a regression analysis was performed. Figure 9, and equations, shows the result of that analysis separately for each group of deafness history and also separately for dorsal and ventral locations of cortical threshold minima. The normal relationship (- - -) between cortical position and cochlear position via the CF relationships in hearing animals also is shown (see Fig. 8).

With the exception of the ventral part of the long-term deafened animals, the regression lines were significantly different from zero and had the same sign as for the normal hearing animals. Consequently, the shift in cortical position with variations of cochlear stimulation locus was consistent with a maintained global cochleotopic gradient. For the dorsal minima in the acute cases and the short-term deafened cases, the slope of the regression was statistically not different from the normal acoustic cases and, thus is reflecting the same cochleotopic gradient in AI as in hearing animals. For the dorsal minima in the long-term deafened cases, the cochleotopic gradient for electrical stimulation was significantly shallower than the gradient in hearing animals and also shallower than the gradients for the acute and short-term cases.

FIG. 4. Reconstruction of cortical response threshold distributions for a short-term deafened case (C325; n = 100). Results for 2 bipolar radial pairs, 1 bipolar longitudinal pair, and 1 monopolar electrode (p1m) are shown. Same conventions as described for Fig. 1. Most apical pair was located ~45% from cochlear base. Interval between iso-threshold contours is 5 dB.
Accordingly, the cochleotopic organization in dorsal AI appears to have deteriorated during long-term deprivation from sound input, although a cochleotopic tendency was still evident. In ventral AI, the distinction between the three groups is less clear. Although the cochleotopic gradient for the short-term cases appears to be the same as for normal hearing animals, the ventral gradient in the acute cases is slightly shallower than normal. By contrast, the ventral gradient for the long-term deafened group is not significantly different from zero, i.e., no cochleotopic organization is evident in this region after prolonged deafness.

It should be noted that the acute and the short-term deafened animals showed, on average, no significant difference between the rostrocaudal location of the threshold minima in dorsal and ventral AI. However, for the long-term deafened animals, there was a significant difference with the ventral threshold minimum located ~0.7 mm more rostrally than the dorsal minimum.

**FIG. 5.** Reconstruction of cortical response threshold distributions for a long-term deafened case (K56, n = 99). Results for 2 bipolar radial pairs (offset), 1 bipolar longitudinal pair, and 2 monopolar electrodes (p1m, p4m) are shown. Same conventions as described for Fig. 1. Most apical pair was located ~51% from cochlear base. Interval between iso-threshold contours is 3 dB.
Effects of electrode configuration and deafness duration on minimum threshold

One of the main questions of this study was whether long-term deafening introduces a decrease in response sensitivity of cortical neurons reflected in an increase of the minimum response threshold in cortex. The lowest response threshold encountered for each electrode configuration and for each case was determined for the dorsal and ventral response minima (see Fig. 10A). Regression analysis showed that the ventral and dorsal minimum thresholds were highly correlated ($R^2 = 0.89$; slope = 0.994, $P < 0.0001$). A paired t-test showed no significant difference between the minimum thresholds in these two cortical subregions. Consequently for the further analysis of threshold differences between electrode configurations and deafness histories, only the absolute minimum was considered without further distinctions between dorsal and ventral locations.

Figure 10B shows the minimum thresholds averaged across the three electrode configuration (□) and across the different deafness durations (■). No significant threshold difference was found between the long- and short-term deafened conditions when averaging across all electrode configurations. However, the thresholds of the acute group differed significantly from the short-term as well as the long-term deafness conditions when including all tested electrode configurations. The acute group had higher thresholds in the range of 6.5–7 dB (Fig. 10B, □). Several factors may have contributed to these differences that will be discussed later. However, one contributing effect may stem from the fact that in the acute group, more radial pairs and, in particular, more basally located electrode pairs were available to be tested than in the other cases. Some of those additional pairs had quite high minimum thresholds, driving up the mean minimum threshold. To test the effect of the inclusion of less effective electrode pairs on the average minimum thresholds, only those conditions were considered that were within 3 dB of the minimum value found for each class of electrode configurations in each case. As a consequence, the average thresholds for the acute group was lowered by 6.4 dB, whereas the short- and long-term thresholds were lowered by <1.5 dB. The analysis of threshold differences between the deafness histories for this selection criterion showed difference values of <2 dB that were no longer statistically significant.

Differences between minimum thresholds for the three different electrode configurations across the deafness histories were found. The radial electrode configurations had significantly higher thresholds than both the longitudinal and monopolar configurations (Fig. 10B, ■). When including all tested electrode configurations, the differences were in the range of 7.5–8 dB, whereas the differences were in the range of 3.6–3.7 dB when only considering the lowest thresholds for each configuration and each case. There was no significant difference between longitudinal and monopolar configurations.
However, it has to be kept in mind that we did not test monopolar configurations in the acute group. There was no statistically significant interaction effect between the electrode conditions and the deafness conditions (see Fig. 10).

In summary, radial electrode pairs had, on the average, a higher minimum threshold than the longitudinal and monopolar conditions, whereas there was no sensitivity difference between longitudinal and monopolar stimulation. Across all stimulation configurations, there was no sensitivity difference between the different deafness groups when only considering the most sensitive electrode configuration per electrode class.

Effects of electrode configuration and deafness duration on extent of low-threshold area

As seen in the previous section, the stimulation effectiveness depended strongly on electrode position and configuration and therefore plays a major role in comparing threshold values between different experimental conditions, such as deafness history. By contrast, the comparison of the spatial distribution patterns for different electrode configurations and deafness histories is less affected because those measures do not appear to be strongly determined by absolute threshold and can be evaluated independent from minimum threshold differences. Indeed it turned out that the differences seen for the descriptors of the spatial activation pattern in AI discussed in the following sections were quite similar when considering either all electrode configurations or only those conditions with the most sensitive response in its electrode class. Accordingly, for the remaining response pattern characteristics, we shall only discuss differences between deafness histories and electrode configurations that are based on all tested electrode conditions combined.

We used several measures of the activated cortical area to evaluate the spatial extent of activation (see METHODS and Fig. 1). For this purpose, the low-threshold area was defined as that region of activated cortex that was within 6dB of the minimum threshold for a given electrode configuration. We expressed this area measure relative to the extent of the total mapped region. Because the mapped region could vary from case to case (see Table 1), the question has to be addressed whether the absolute size of the mapped areas influenced the obtained differences between different experimental conditions. Regression analysis between map size and size of the low-threshold area showed no significant correlation. Combined with the fact that the map size between the cases of the different deafness histories was not significantly different (see preceding text), the use of a relative measure of cortical activation area can be justified.

The mean extent of the low-threshold area is shown in Fig. 11A separately for the different deafness durations and the different electrode configurations. The smallest activation area was found for the acute conditions (across all electrode configurations), and the largest area was found for the short-term deafness condition. The average short-term area was more than twice the size of the average area in the acute cases. The activation area for the long-term condition was significantly larger than the acute conditions and slightly but significantly smaller than in the short-term conditions. It is concluded that the overall size of cortical area activated at low stimulus levels is not solely dependent on the duration of deafness or, implicitly, number of surviving spiral-ganglion cells in the cochlea.

Across all deafness histories, the radial configuration showed the smallest low-threshold activation area, whereas the areas for both the longitudinal and the monopolar conditions were 1.5 times larger and not significantly different from each other. A factorial ANOVA test for activation area revealed no interaction between electrode configuration and deafness duration (Fig. 11B).

FIG. 8. Characteristic frequency (CF) vs. cortical distance from 8 normal hearing animals (n = 689). For pooling across cases, slopes for the logarithm of CF of individual animals were normalized to the average slope. Distance origin was set relative to position at CF = 6.5 kHz.
Effects of electrode configuration and deafness duration on spatial tuning width

Although the area of low-threshold responses is a useful measure of the extent of cortical activation, special attention has to be given to the spread of excitation along the cochleotopic axis. Such a measure can be more suitable for considerations of important stimulation aspects in cochlear implants such as channel interaction and activation overlap than the areal measure. Accordingly, the measure of “spatial tuning width” has been used in other auditory stations (e.g., Kral et al. 1998; Snyder et al. 1990) (note that this measure refers to the spatial extent of activation in auditory stations and is not to be confused with measures of sound localization receptive fields). In the case of the auditory cortex, two spatial tuning measures have to be considered, namely, one for the dorsal activation region and one for the ventral region. Three examples of spatial tuning curves are shown for radial electrode configurations in Fig. 12. Rostrocaudal cross-sections across the dorsal threshold minimum are shown for an acute case (□; C163; p5,6), a short-term deafened case (*; C637; p2,3), and a long-term case (○; K56; p3,4). The cortical distance axis is given relative to the position of the threshold minimum. The spatial tuning width is marked 6 dB above minimum threshold (---, ---, and --->). These examples demonstrate that the spatial tuning width can vary over a wide range across the three experimental conditions.

The mean spatial tuning width for the different conditions are shown in Figs. 13 and 14 for dorsal and ventral AI.
respectively. Across all electrode configurations, the acute cases were significantly more narrowly tuned than the long-term and the short-term cases for both dorsal and ventral AI. In contrast to the activation area, there were no differences in spatial tuning width between long- and short-term deafening.

Across all deafness groups, the radial electrode configurations showed narrower tuning than the longitudinal configuration in ventral AI but not in dorsal AI. This difference was also significant for the dorsal part of AI when only considering the acute cases (Fig. 13). However, it appears that these differences were largely due to several very narrowly tuned acute cases. When the acute cases are excluded from the comparison, no significant difference between different electrode configurations can be seen. There were no significant differences in spatial tuning between the longitudinal and monopolar electrode configurations for the short- and long-term cases. No interaction between configuration and deafness duration was evident (Figs. 13B and 14B).

Effects of electrode configuration and deafness duration on high-threshold ridge

A common feature in the distribution of activity across AI was a narrow ridge of high-threshold or unresponsive locations spanning usually the whole rostrocaudal length of the mapped areas. This ridge separated the dorsal from the ventral low-threshold regions (see Figs. 2–6). The width of the ridge measured along the dorsalventral axis 12 dB above minimum threshold varied quite dramatically between some of the configurations. Examples of cross-sections of the central high-threshold ridge are illustrated in Fig. 15 for radial electrode configurations. Ventral-dorsal threshold-profiles running through the dorsal and/or ventral threshold minima are shown for an acute case (C163; p5,6), a short-term deafened case (*; C325; p3,3a), and a long-term case (K56; p3,4). The width of the ridge is indicated (---). In a few cases, no central ridge could be observed, or the ridge showed interruptions that prevented fulfillment of the criteria to establish a width measure. Usually the ridge width was determined along a line between the dorsal and ventral location with the lowest threshold that was oriented perpendicular to the main direction of the ridge. The mean width of the central ridge is shown in Fig. 16 for different deafness durations and different electrode configurations. Quite substantial differences in the ridge width were seen between the acute cases and the short-term cases with an average width for the short-term cases of <25% of the acute cases. An almost equal difference was seen between long- and short-term cases, whereas acute and long-term cases were not significantly different.

For the different electrode configurations, the only significant difference in the ridge width was that the radial configura-
ration produced a broader ridge than the monopolar configurations. This difference is still evident when only considering the short- and long-term cases, since no monopolar conditions were tested in the acute cases. There was no statistically significant interaction between electrode configuration and deafness duration (Fig. 16B).

Does chronic electrical stimulation influence activation parameters in long-term deafened animals?

Two of the five long-term deafened animals (K55 and K56) received chronic electrical stimulation of the cochlear implant for 2–4 mo immediately before the electrophysiological evaluation of cortex (see METHODS). Prolonged chronic stimulation in younger animals has been reported to result in changes in the spatial pattern and other response characteristics in the inferior colliculus (Snyder et al. 1990) and the auditory cortex (Dinse et al. 1997b). The cortical response parameters for these two animals were mostly within the range of the unstimulated animals. Only K56 had slightly higher thresholds and a smaller area of activation than the other long-term cases. To test whether exclusion of these two animals from the comparative analysis of the deafness groups would change the general conclusions drawn for all five long-term animals, we repeated the factorial ANOVA analysis without the stimulated cases. Although some of the mean parameter values for the long-term group changed slightly, the pattern of statistically significant differences between the deafness groups and the electrode groups remained unchanged. The effects of chronic electrical stimulation on cortical responses will be presented elsewhere in detail and for a larger group of animals.

Correlation analysis of parameters

A correlation analysis between the main measures across all electrode and deafness conditions is useful to estimate the shared information provided by the different, often arbitrarily selected response descriptors. This analysis revealed a number of covariances between measures of response sensitivity, cortical location of activation, and extent of activation. The correlation coefficients and the significance values are shown in Table 2. Not surprisingly, all measures taken independently for dorsal and ventral AI, such as minimum threshold, spatial...
tuning width, and rostrocaudal position, were highly correlated (see Table 2). Measures of cortical extent of activation, namely spatial tuning width, low-threshold area, and width of the high-threshold ridge, moderately covaried. The wider the spatial tuning, the larger was the activation area and the narrower was the high-threshold ridge. Additionally, there was a modest correlation between response threshold for either dorsal or ventral AI and the rostrocaudal position of the minimum threshold in dorsal AI but not in ventral AI. Weak correlations existed between most parameters with the exception of the rostrocaudal position of minimum threshold in ventral AI, which appeared not to be correlated with any of the other parameters other than the dorsal position. The dorsal minimum threshold was also independent from dorsal spatial tuning.

To determine objectively which of the obtained measures of the spatial excitation patterns provide necessary and independent information, a principal component analysis was performed for all electrode configurations and deafness durations. From the eight response measures (see Table 2), three orthogonal or independent factors (Eigenvalues < 1.0) emerged that...
accounted for 80% of the total variance of the data. The parameters associated with the different factors all had a load on their corresponding factors >0.56, i.e., the variance in the factor values accounted for ≥75% of each contributing parameters variance. The grouping of the parameters reflects the strength of correlations between the parameters as given in Table 2. The strongest factor (F1) accounted for 46% of the total variance and comprised four measures related to areal aspects of the activation pattern: low-threshold area (load: 0.89), spatial tuning width for ventral (0.84) and dorsal (0.81) AI, and the width of the high-threshold ridge (−0.60). The second strongest factor (F2) accounted for 20% of the variance and corresponded to three parameters: minimum response threshold in dorsal (0.95) and ventral (0.93) AI and the rostrocaudal position of the dorsal threshold minimum (0.59). F2 was dominated by response sensitivity measure but also reflected a moderate correlation between cochleotopic position and response threshold. The remaining factor (F3, 14% of variance) was composed of the rostrocaudal position of the ventral (0.96) and dorsal (0.66) threshold minima reflecting the overall cochleotopic organization of AI. The dorsal position measure was the only one that contributed about equally to more than one factor (F2 and F3).

In summary, across all experimental conditions the measures applied in this study captured three independent factors, namely, position, extent, and sensitivity of cortical activation by cochlear electrical stimulation. However, because of the spatial complexity of the activation pattern, the use of several measures for extent and shape of the activation distribution can be useful.

**DISCUSSION**

The goal of this study was to evaluate parametrically the extent of cortical activation by peripheral electrical stimulation with a particular emphasis on studying the effects of different lengths of deafness duration on neuronal response threshold in the adult cat. The first group was composed of animals that were deafened shortly after birth, and, with the exception of two animals, had only the most minimal experience with sound over their lifetimes. The comparison groups were adult animals with normal hearing experience that were studied acutely or deafened 2 wk before being studied. The interaction of elec-

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**FIG. 15.** Central high-threshold ridge. Three examples of a central high-threshold ridge are shown for radial electrode configurations. Ventrodorsal slices near the dorsal and ventral threshold minima are shown for an acute case (●; C163; p5.6), a short-term deafened case (*; C325; p3.3a), and a long-term case (¥; K56; p3.4). Position of the cortical distance axis is arbitrary. - - -, ridge width 12 dB above minimum threshold.

**FIG. 16.** Bar graphs of mean width for central high-threshold ridge. For each case (n = 17), the width of the horizontal ridge in central AI was determined that separates dorsal and ventral low-threshold regions. Dorsoventral ridge width was determined near the line connecting the locations of minimum threshold in dorsal and ventral AI 12 dB above lowest threshold. A: mean ridge width for different deafness durations across all electrode configurations (●) and for different electrode configurations across all deafness histories (¥). B: mean ridge width for different deafness durations separated into subgroups for electrode configurations. Statistically significant differences between conditions are indicated by brackets (*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001).
trode configuration with deafness duration and response threshold was an integral part of the study as well.

These studies demonstrated two circumscribed regions of low response thresholds to cochlear stimulation on the ectosylvian gyrus. These two regions are separated dorsally by a narrow ridge of high response thresholds. Although details of the spatial patterns of threshold representation varied considerably across deafness histories and electrode configurations, this functional partition reflects some general principles regarding the spatial organization of AI for the response sensitivity to cochlear electrical stimulation. The functional tripartition of AI is a particularly interesting finding because it appears to reflect a partitioning of the dorsalventral or iso-frequency domain of AI that has been noted for acoustical stimulation (Schreiner and Mendelson 1990; Schreiner et al. 1992; Sutter and Schreiner 1995). In the acoustic case, dorsal and ventral AI are separated by a band of neurons, running rostrocaudally, with low thresholds and narrow frequency tuning. Neurons dorsal and ventral to this band demonstrate generally higher thresholds and often broader tuning. The cortical distribution pattern seen with electrical cochlear stimulation reveals essentially an opposite threshold pattern from that of the acoustic domain: a narrowband of high-threshold locations is located between two larger areas of low thresholds (Raggio 1992). The consistent finding of elongated patches alternating between high and low response thresholds that are oriented along the cochleotopic axis strongly suggest the existence of a system of functional modules in AI.

The phenomenon of electrically evoked tonotopicity has been demonstrated in early work by Woolsey and Walzl (1942) and, more recently, by Volkov and Dembnoteskii (1979) using evoked potential methodology. They were able to demonstrate a point-to-area representation of cochlear nerve fibers in the cortex. Interestingly, Volkov and Dembnoteskii (1979) showed two regions with large evoked response amplitudes in the area most likely corresponding to AI. These areas of high-amplitude, short-latency responses were found in dorsal and ventral AI regions. Apparently, the distance between the corresponding dorsal and ventral regions varied significantly across these adult, acutely studied animals but remained constant from one cochlear stimulation position to the next for the same animal. It is likely that these two evoked-potential regions correspond to the two low-threshold regions seen in this microelectrode study. Before discussing potential causes and consequences of such an organization and the influence of deafness duration on this pattern, some methodological issues have to be addressed.

**Identification of cortical location**

In normal hearing animals, the reliable identification of cortical recordings sites, viz. specific auditory cortical fields, usually is based on the local tonotopic gradient rather than on sulcal landmarks. The reason is that the exact position and extent of the sulcal pattern can vary substantially relative to the frequency organization of a given field (Merzenich and Schreiner 1992; Merzenich et al. 1975; Reale and Imig 1980). Accordingly, it is difficult to verify precisely the location of a cortical field with electrical stimulation of just a few cochlear sites. However, several lines of arguments suggest that most recording locations in this study were indeed located in AI with only a few locations at the edge of the mapped area located in the AII and the anterior auditory field (AAF). In the acutely deafened animals, we were able to determine electrophysiologically the layout of AI with acoustic stimulation before the implantation (Raggio 1992), thus ensuring that the remapping with electrical stimulation was largely limited to locations within AI. The map/remap procedure allows a direct comparison of the spatial distribution of acoustic and electric receptive field parameters as will be reported in detail elsewhere. In the short- and long-term deafened animals, this direct comparison was not possible. However, the short-term group showed clear evidence of cochleotopic organization across the mapped region when changing the stimulation position in the cochlea. The resulting sign and slope of the gradient is consistent with the normal frequency organization of AI. Additionally, the comparison between acoustic and electrical stimulation in the acute group revealed that the central high-threshold ridge seen with electrical stimulation corresponded closely to the sharply tuned, low-threshold region in hearing animals and was located approximately at the dorsoventral center of AI (Raggio 1992). Because the high-threshold ridge in the short-term and, in particular, the long-term group usually was found near the center of the mapped area and also within a few millimeters of the dorsal end of the ectosylvian sulci, it is reasonable to assume that most of the mapped regions indeed are largely representing properties of AI.

Because the goal of the study was to determine the position and extend of cortical activation evoked by electrical stimulation, the use of the multiple unit method to obtain neuronal responses is sufficient. For each recording location, the neuron with the lowest threshold of the cluster determined the threshold measurement. Such an approach is quite efficient because it cannot be assumed that all neurons within the recording region have the same response properties or thresholds. Ac-
cordingly, the cluster response provides a higher probability to find the local minimum threshold than single unit recordings (see also Schreiner and Mendelson 1990; Schreiner et al. 1992). The behavior of single cortical units in response to peripheral electrical as compared to acoustic stimulation has been described previously in some detail (Raggio and Schreiner 1994; Schreiner and Raggio 1996).

Cochleotopicity

The current study shows a clear cochleotopic gradient in AI for electrical cochlear stimulation of adult animals that were either acutely implanted or had only two weeks of deprivation from auditory input. Both dorsal and ventral regions of AI show the same slope of cochlear position versus cortical position as normal, hearing animals. By contrast, the long-term deafened animals show no gradient or a much shallower gradient than normal or short-term deafened animals. It is concluded that long-term deafening, or the sustained absence of auditory input, and the profound reduction in intrinsic optical recordings also confirmed a basic cochleotopic organization of the spatial distribution of activation reflected by the optical gradient in acutely implanted animals. In addition, inspection of at least a rudimentary gradient than normal, cochleotopically appropriate region of low threshold activity. The area of low-threshold activation was the smallest for the acute animals, and the width of the high-threshold ridge was greater than for either of the other two groups.

Auditory cortical neurons of animals that are hearing into adulthood and are acutely deafened at implantation demonstrate a threshold pattern quite similar, in terms of tonotopic representation, to that seen using acoustic stimulation in a hearing animal. It may be that because of the short time between deafening and studying the animal that we were unable to witness any clear reorganization of neuronal response distributions. It also may be that these animals have maintained some of their hair cells, so that some activation via remaining hair cells may be contributing to the overall response. However, previous studies indicate that responses from overt electrical stimulation of hair cells usually have a higher activation threshold than the direct stimulation of ganglion cells or axons (Hartmann et al. 1984; Kral et al. 1998; van den Honert and Stypulkowski 1984). Furthermore insertion of the electrode is likely to damage or destroy a percentage of the hair cells as reflected in a steep decline of response thresholds to acoustic stimulation in the hours after implantation (R. Hartmann, personal communication). However, it is not clear how various degrees of hair cell damage may have contributed to the relatively large variance in the extent of activation seen in the acute group. Spatial tuning and minimum threshold in ICC neurons from electrical stimulation of a cochlea with large hair cell survival were found to be indistinguishable from deafened animals (P. Leake and R. Snyder, personal communication).

Taken together, these arguments support the conclusions that the observed spatial distribution of cortical activation in acutely implanted animals is a true reflection of the cortical functional organization to focal electrical cochlear stimulation and reflects only minor effects from the electrophonic or other secondary stimulation effects.

The physiological picture provided by the animals deafened from birth was one of relatively low thresholds with a moderate increase of the area of activation, a largely diminished representation of cochleotopicy, and a distinct high-threshold ridge in the center of AI. The threshold distribution pattern was in some cases more patchy and less circumscribed than the acute or short-term groups, although relatively organized patterns were encountered as well. In spite of many years of deafness and the subsequent loss of spiral ganglion cells, the animals deafened at birth were still able to maintain a quite normal threshold range and a spatially restricted activation area, albeit larger than in the acute cases. The relatively low response thresholds were somewhat surprising because the spiral ganglion density in these animals was reduced to \( \approx 9\% \) of normal animals (P. Leake, personal communication). Previous studies in animals and humans have suggested that the loss of spiral ganglion density is largely responsible for an increase in response threshold (e.g., R. E. Beitel, R. L. Snyder, C. E. Schreiner, M. W. Raggio, and P. A. Leake, unpublished observations; Pfingst et al. 1981; Shepherd and Javel 1997). Although thresh-
old increase as a consequence of spiral ganglion loss is a reasonable assumption, it is conceivable that such a threshold increase may be particularly expressed under stimulation conditions that are more challenging for the system, such as at high repetition rates of the stimulus. Other influences that may have contributed to the fairly low thresholds in the cortex of long-term deafened animals may be related to electrode differences between the experimental groups, with relatively narrowly spaced, pure radial, and small electrode contacts in the acute case, versus slightly bigger and off-radial electrodes in the long- and short-term cases.

The short-term group was designed to control for two parameters that potentially influenced the findings in the acute group while maintaining one of the most important aspects of the comparison groups, namely a nearly complete survival of the spiral ganglion. First, the animals received treatment with aminoglycoside antibiotics sufficient to generate widespread damage to hair cells (Leake et al. 1987; Xu et al. 1993). Second, the 2-wk period between electrode implantation and physiological experiment served to improve the conditions for electrical stimulation by, for example, gradual removal of air pockets around electrode contacts that may have impeded stimulation in the acute implantations (R. Snyder, personal communication), as well as providing a comparable situation to that found in the long-term deafened animals.

The responses for the short-term animals shared some physiological characteristics with the acute animals, some with the long-term animals, and some with neither. This group demonstrated an area of low threshold that was the largest of any group but had a spatial tuning width similar to the long-term animals. On the other hand, the cochleotopic representation of electrode stimulation position was the same as for the acute group, i.e., near normal. The width of the high-threshold ridge in the center of AI was markedly narrower for the short-term group than acute but was again similar to the long-term group. In other words, this group demonstrated cochleotopic organization similar to normal animals, but its other characteristics were more aligned with animals that had been deafened for some time.

One potential explanation for these unexpectedly large differences between the acute and short-term groups is that the cortical neurons of the latter group, having been deprived of sound stimulation for 2 wk before study, were undergoing an initial reorganization of neuronal inputs by adjusting excitatory and, in particular, inhibitory processes. Loss of inhibition after peripheral deprivation of sensory input has been described in the visual and somatosensory cortices (e.g., Garraghty et al. 1991; Hendry and Jones 1986). Rajan (1998) reported that even mild hearing loss may result in a profound alteration of the inhibitory strength reflected in auditory cortical neurons. In the case of electrical stimulation, a similar reduction in inhibitory strength may be the cause of the relative reduction of response thresholds in the usually higher threshold center ridge compared with the acute and long-term cases. Reduction in inhibition also could be responsible for the observed increase in the rostrocaudal extent of activation in AI for the long-term and, in particular, short-term deafened animals. However, it appears that the initially reduced inhibition may be restored partially over time because the long-term deafened animals show a more strongly expressed high-threshold area in the center of AI. Additionally, the size of the rostrocaudal extent of activation did not differ between the short-term and long-term groups, and other mechanisms than lack of inhibition may contribute to the broadening of spatial tuning in these two groups. Some of these other factors may be found in the large variability of response properties that are caused by variations in electrode design, electrode placement relative to the spiral ganglion, and overall local condition for electrical stimulation.

The high response thresholds in the central ridge region are likely the consequence of strong inhibitory effects. It appears (Raggio 1992) that this region coincides with the most sharply tuned region in AI of normal-hearing animals. One of the mechanisms that contribute to the generation of sharp frequency tuning in that region is the presence of strong inhibitory side-bands (Sutter et al. 1999). The side-bands already are reflected in the thalamocortical projection to this region but may be strengthened by intrinsic cortical mechanisms as suggested by a relatively high local density of GABAergic neurons in or near this region (Frieto et al. 1994). Recent studies of the effects of cortical application of bicuculline, a GABAa antagonist, support this view by demonstrating a clear broadening of the frequency response areas (Taha et al. 1996; Wang et al. 1996). This strong inhibitory influence results in fairly weak responses to broadband stimuli predominantly in cortical regions of sharp tuning (Schreiner and Mendelson 1990). However, the response thresholds in normal hearing animals can be low even for broadband stimuli. The consistently high thresholds along the central ridge for electrical stimulation reflect therefore not only the consequence of a relatively broad peripheral excitation pattern in combination with strong inhibitory side-bands. They also reveal that some additional mechanisms must be operative for acoustic input that are not properly invoked with electrical stimulation. For example, the unnatural high synchrony of the input across the cochleotopic input array with electrical stimulation (Kral et al. 1998; Raggio and Schreiner 1994; Schreiner and Raggio 1996; van den Honert and Stypulkowski 1987) may give rise to a violation of specific coincidence requirements and may result in a failure to evoke responses in circumscribed parts of AI.

Modular organization of AI

As mentioned earlier, the quite reliable feature of functional banding across AI into regions with high and low response thresholds lends further support to the notion that AI is not functionally uniform but may show functionally distinct subregions or functional modules. Previous studies have provided physiological (e.g., Heil et al. 1992; Schreiner and Mendelson 1990; Schreiner and Sutter 1993; Schreiner et al. 1992; Sutter and Schreiner 1995) and anatomic (Read et al. 1998) evidence for the existence of such modules in hearing animals. These modules may provide an organizational frame work for the processing and may even give rise to different processing streams not unlike those seen in the visual system for shape and motion processing (Mishkin et al. 1983). In this study, we showed that such a modular structure is present after many years of deafness and without much auditory experience. It is still present when the cochleotopic organization is largely absent. However, in several long-term deafened animals, the spatial uniformity of the bands was compromised, suggesting that position and content of the bands may undergo reorganizational changes. It also should be noted that we only found a single high-threshold band across AI. By contrast, physiological (Schreiner and Mendelson 1990; Schreiner and Sutter 1993; Sutter and Schreiner 1996) and anatomic (Read et al. 1998) evidence
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1998) evidence from hearing animals points to a second band of sharp tuning, located more dorsally and parallel to the central, sharply tuned (acoustical) and high-threshold (electrical) region. Because this dorsal band was not clearly evident with electrical stimulation, despite extensive mapping up to the supra sylvian sulcus, it suggests clear physiological distinctions between the dorsal and central bands of narrowband frequency tuning.

Potential consequences for cochlear implants

One purpose of this study was to establish the long-term effects of deafness on cortical organization as revealed by electrical cochlear stimulation. This is a first step for the evaluation of the effects of potential rehabilitation strategies on auditory cortical structures. Three aspects of the results appear to be of special interest in this context. First, responses in auditory cortex to electrical stimulation were strong, crisp and had nearly normal minimum thresholds despite the fact that the long-term deafened animals had <10% spinal ganglion survival. Although variations in electrode design may have obscured some minor threshold shifts with deafening, our observations provide some boundaries for the, to be expected, sensitivity changes with massive loss of peripheral innervation density. Second, a clear deterioration of cochleotopic organization with long-term deafness was observed with electrical stimulation. This strongly suggests that deleterious effects of “channel interactions” are not limited to physical interactions at the peripheral interface but that central auditory reorganization may contribute as well. In other words, even with perfect channel separation in the peripheral auditory system, the observed loss of channel segregation in long-term deafened animals would still limit the information flow to speech and language cortex. However, it is conceivable that appropriate perceptual and behavioral training strategies may be employed (e.g., Buonomano and Merzenich 1998) to invoke a functional reorganization of auditory cortex for restoring a sufficient central channel separation. Third, the observation of a modular structure along the dorsalventral axis of AI for electrical stimulation suggests that basic functional circuits in auditory cortex remain operational even after significant auditory deprivation. This preservation of functional organization and diversity might be of great advantage for successful rehabilitative efforts. Noninvasive assessment of the status of such an organization may provide a tool for determining the prognosis for the success of a cochlear implant when used in combination with other measures such as the status of the spiral ganglion density.

Overall, this detailed assessment of the responsiveness and organization of the cortical responsibility distribution in deafened animals provides further evidence of a modular functional organization of AI and establishes the necessary foundation for the exploration of the effects of different strategies of chronic electrical stimulation for the full restoration of central auditory functions.

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