Plasticity of Frequency Organization in Auditory Cortex of Guinea Pigs With Partial Unilateral Deafness

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ABSTRACT

We have examined the effect of restricted unilateral cochlear lesions on the orderly topographic mapping of sound frequency in the auditory cortex of adult guinea pigs. These lesions, although restricted in spatial extent, resulted in a variety of patterns of histological damage to receptor cells and nerve fibres within the cochlea. Nevertheless, all lesions resulted in permanent losses of sensitivity of the cochlear neural output across a limited frequency range. Thirty-five to 81 days after such damage to the organ of Corti, the area of contralateral auditory cortex in which the lesioned frequency range would normally have been represented was partly occupied by an expanded representation of sound frequencies adjacent to the frequency range damaged by the lesion. The thresholds at their new characteristic frequencies (CFs) of clusters of cortical neurones in these regions were close to normal thresholds at those frequencies (mean difference across all animals was 3.8 dB). In a second series of experiments, the responses of neurone clusters were examined within hours of making similar cochlear lesions. It was found that shifts in CF toward frequencies spared by the lesions could occur, but thresholds were greatly elevated compared to normal (mean difference was 31.7 dB in five animals). The emergence of sensitive drive in such regions after prolonged recovery periods in lesioned animals thus suggests that the auditory cortical frequency map undergoes reorganization in cases of partial deafness. Some features of this reorganization are similar to changes reported in somatosensory cortex after peripheral nerve injury, and this form of plasticity may therefore be a feature of all adult sensory systems.

Key words: cochlear lesions, hearing loss, cortical maps, tonotopicity, adult, mammal

Topographic representation of the receptor surface on the cerebral cortex is a general feature of the major sensory systems. There is accumulating evidence that such topographic representations can be modified in the adult brain, as well as in the course of development, by removal of input from limited regions of the receptor surface. Studies of the topographic representation of the body surface in adult mammalian somatosensory cortex have shown that if afferent input from one part of the skin is removed by transection of a peripheral nerve or amputation of a digit, the deprived area of cortex becomes progressively responsive to neighbouring skin regions (Franck, '80; Rasmusson, '82; Merzenich and Kaas, '82; Kaas et al., '83; Merzenich et al., '83a,b, '84; Jenkins and Merzenich, '87).

It is important for two reasons to know if similar plasticity of cortical representations occurs in the auditory nervous system: firstly, because common cases of partial deafness in adult humans involve an analogous reduction of input from a restricted region of the receptor surface, the organ of Corti (Bredberg, '68). Secondly, the demonstration of such plasticity in the auditory system, despite the greater complexity of the ascending pathways compared to the somatosensory

system (Warr, '82; Aitkin et al., '84; Irvine, '86), would provide a test of the generality of such effects.

In the auditory system, sound frequency is represented systematically along the length of the auditory receptor organ, the organ of Corti. Topographic representation of the receptor surface within the central nervous system results in an orderly mapping of sound frequency in core auditory cortical fields (Knight, '77; Merzenich and Brugge, '73; Merzenich et al., '75; Imig et al., '77; Hellweg et al., '77; Reale and Imig, '80; Aitkin et al., '86; Redies and Creutzfeldt, '87). We have examined cortical frequency maps in normal animals and in animals in which localized lesions of the organ of Corti have resulted in reduced input to the central nervous system from restricted frequency domains of the receptor surface.

MATERIALS AND METHODS
General surgical procedures

Experiments were carried out on adult pigmented guinea pigs of both sexes, obtained from the colony at Monash University. Animals ranged in weight from 260 to 840 g. During all surgical and recording procedures, animals were anaesthetized and allowed to breathe unassisted. They were held in a custom-made head holder with hollow ear bars. This allowed ready access to the cochlea and auditory cortex. Rectal temperature was maintained between 37.5 and 38.5°C with a thermostatically regulated heating pad.

All animals were given 100 μg atropine sulphate subcutaneously and were anaesthetized by intraperitoneal injection of 30 mg/kg of pentobarbitone sodium (Nembutal) followed by intramuscular injection of Innovar-Vet (fentanyl citrate, 0.4 mg/ml, droperidol, 20 mg/ml) to achieve a surgical level of analgesia and anaesthesia. All incisions were infiltrated with local anaesthetic (1% Xylocaine for injection, or 10% Xylocaine topical spray). In acute experiments, intubation of the trachea was performed. In some animals, the right internal jugular vein was cannulated for administration of supplementary doses of anaesthetics, while in others these were administered by intraperitoneal and/or intramuscular routes. Supplementary doses of anaesthetics were given ad libitum to maintain deep surgical anaesthesia throughout the experiments. In a number of animals intravenous administration of dextrose and/or saline was used in an attempt to maintain systemic blood pressure during long recording sessions. In animals in which cortical recordings were to be made, 0.5 ml of Decadron (dexamethasone sodium phosphate) was administered intramuscularly 12 hours prior to the experiment in an effort to control cerebral oedema.

CAP audiograms

In all animals, after inspection of the tympanic membrane, the left tympanic bulla was opened and the sensitivity of the left cochlea to acoustic stimuli was assessed by the compound action potential (CAP) audiogram. Tone bursts (5/second; 20 ms duration with 0.5 ms rise-fall times) were generated as described in previous reports (Wise and Irvine, '83; Aitkin et al., '86) and delivered via condenser microphone drivers coupled to the ear bars. The CAP audiogram technique, which has been described in detail previously (Johnstone et al., '79), measures the threshold of the gross response of the auditory nerve to tone bursts ranging in frequency from 2 to 30 kHz. It provides an accurate index of the sensitivity of the cochlear neural output over this fre-

quency range (Dallos and Cheatham, '76; Ozdamar and Dallos, '78; Johnstone et al., '79; Harris, '79; Cody et al., '80). The CAP audiogram was compared to a large normal data base (Cody and Robertson, '83) and was used to 1) reject animals with initially abnormal cochlear sensitivity, 2) monitor the status of the cochlea during long recording sessions, and 3) assess the peripheral consequences of the mechanical lesions of the cochlea used to produce partial deafness.

The CAP audiogram was also used in one animal to assess the level of interaural crosstalk by comparing the sound pressure required to reach CAP threshold when sound was applied through either the ipsilateral or the contralateral ear bar. It was found that between 6 and 30 kHz, the interaural attenuation was in excess of 60 dB.

Cortical mapping

The right auditory cortex was exposed by partial craniotomy and the dura mater was removed. Immediately after exposure, several drops of Sofradex (topical dexamethasone solution) were applied to the cortical surface. A well of Vaseline filled with silicone oil was constructed over the exposed area of cortex to prevent drying out of the cortical surface.

The frequency organization of the auditory cortex was established by conventional neurone cluster mapping techniques reported in detail elsewhere (Merzenich et al., '75; Aitkin et al., '86). Multiple penetrations spaced approximately 200 μm apart were made normal to the cortical surface with glass-insulated tungsten microelectrodes, and the responses of clusters of cortical neurones to tone burst stimulation (1/s; 100 ms duration with 5 ms rise-fall times) of the left cochlea were recorded. Responses were recorded at one or more depths in the range 300–1,000 μm from the cortical surface. At each point, the sound frequency at which cluster threshold was lowest (characteristic frequency; CF) was determined by using audiovisual criteria. The location of each penetration was marked on a high-resolution photograph of the cortical surface vasculature. As a routine control procedure, the experimenter making CF determinations was unaware of the exact location of individual penetrations. At the end of the experiment the animals were killed by overdose of Nembutal, and if required, the left cochlea was removed for histological processing.

Cochlear lesions

In two groups of animals, partial unilateral deafness was produced by direct mechanical lesion of a restricted portion of the organ of Corti by using techniques reported in detail elsewhere (Robertson et al., '80). Under anaesthesia, a small hole was drilled in the bony wall of the scala tympani of the basal cochlear turn and a glass pipette with a tip diameter of about 50 μm filled with 150 mmol/liter KCl was introduced through the hole and into the organ of Corti and scala media. Entry of the pipette into scala media was signalled by the appearance of the large positive endocochlear potential (Kjuipers and Bonting, '70; Sellick and Johnstone, '75) recorded between the pipette tip and a silver wire placed in the neck muscles. The CAP audiogram was monitored and the procedure was repeated until a significant elevation of neural thresholds occurred in a restricted frequency range.

In eight chronic animals (260–500 g, mean weight 317 g) the hole in the scala tympani wall was sealed with a small piece of Gelfilm, the wounds were closed with surgical silk, and the animals were allowed to recover for periods ranging from 35 to 81 days. The final weights of these animals ranged from 520 to 770 g with a mean weight of 661 g. At the

end of the recovery period, the CAP audiogram was again measured to assess the extent of peripheral hearing loss prior to cortical mapping. The frequency organization of the contralateral auditory cortex was then mapped in these animals in the normal fashion.

At the end of cortical recordings the animal was killed by Nembutal overdose, and the left cochlea was removed and fixed by perfusion with 2.5% glutaraldehyde in 0.1 mol/liter phosphate buffer, pH 7.4, followed by 1% osmium tetroxide in 0.1 mol/liter phosphate buffer, pH 7.4. The bony wall overlying the cochlear epithelium was thinned down and removed and the cochlea was dehydrated and embedded in araldite. Whole mounts of half-turn lengths of the organ of Corti were then prepared and examined by interference-contrast microscopy. All hair cells in the basalmost 8 mm of the cochlea were examined and scored as present or absent. Remaining hair cells were further classified as normal or abnormal on the basis of the organization of the stereocilia bundles on their apical surface (Robertson, '82; Cody and Robertson, '83). The number of missing and damaged cells was expressed as a percentage of the normal hair cell numbers in this region of the adult guinea pig cochlea (Cody et al., '80). The location of missing and damaged hair cells was measured relative to the basal end of the basilar membrane. Maps of hair cell damage vs. distance along the cochlea (cochleograms) were constructed and aligned with a sound frequency scale by using the well-established place-frequency map of the tonotopic organization of the guinea pig cochlea (Wilson and Johnstone, '75; Robertson and Johnstone, '79; Robertson et al., '80; Robertson, '84). Degeneration of primary afferent nerve fibres in the osseous spiral lamina was also noted although quantitative counts of fibre numbers were not made.

A second group of animals was used in acute experiments to assess the immediate rather than the long-term effects of a cochlear lesion on cortical frequency organization. Partial frequency maps of contralateral auditory cortex were made before and immediately after cochlear lesions made as described above. These animals were not allowed to recover, and the cochleas were not removed for histological assessment.

RESULTS
Normal cortical maps

The frequency organization of auditory cortex in normal adult guinea pigs was determined in ten animals ranging in weight from 260 to 730 g. The mean CAP audiogram and the variability in CAP thresholds in these animals are shown in Figures 7 and 8. The overall shape and sensitivity of the mean curve agree qualitatively with previous results in adult guinea pigs (Johnstone et al., '79; Cody and Robertson, '83).

In these normal animals, the auditory cortex was found to contain at least two orderly frequency representations, in accordance with the maps obtained by Hellweg et al. ('77). Hellweg et al. ('77) referred to these representations as auditory areas I and II. We shall use the designations rostral and caudal cortical fields. Detailed maps from several animals will be used to illustrate the essential features. As illustrated in Figure 1A a rostral field, the rostral edge of which lies close to the lateral sulcus, has a frequency organization in which low frequencies are represented ventrorostrally and progressively higher frequencies are represented dorsocaudally. Estimated isofrequency contours (lines joining points
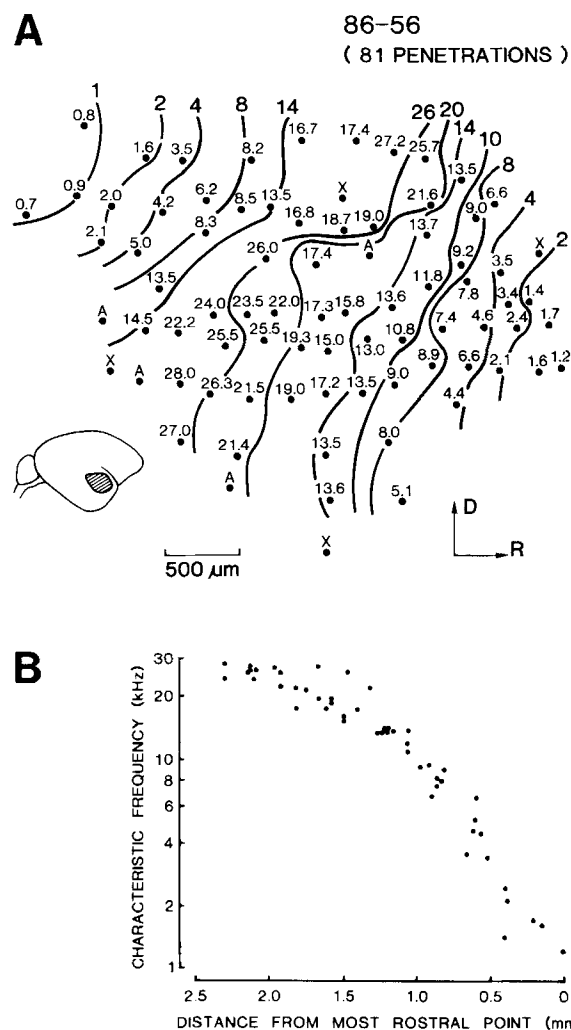

Fig. 1. A: Frequency organization of the auditory cortex in a normal 730 g animal (86-56). Each dot represents the location on the cortical surface of an electrode penetration. Number beside each dot is the CF in kHz of clusters at that point. Points marked X were unresponsive to acoustic stimulation. Points marked A were acoustically responsive, but a clear CF could not be assigned. Lines are approximate isofrequency contours drawn by eye through loci of same CF as indicated by numeral at end of each line. Insert: Approximate location of mapped area. R, rostral; D, dorsal. B: Data in A plotted graphically: CF is plotted as a function of distance from the most rostral point at which a CF was assigned, for the rostral field only. Distance was measured along an axis as near as possible at right angles to the isofrequency contours.

of approximately the same CF) have irregular trajectories, but an approximately dorsorostral-to-ventrocaudal orientation. Caudal to the high-frequency edge of this field there is a progressive decrease in CF, defining a second field with an approximately mirror-image frequency organization, which we have termed the caudal field.

A plot of CF as a function of distance along an axis approximately orthogonal to the estimated isofrequency contours is presented in Figure 1B for all points in the ros-
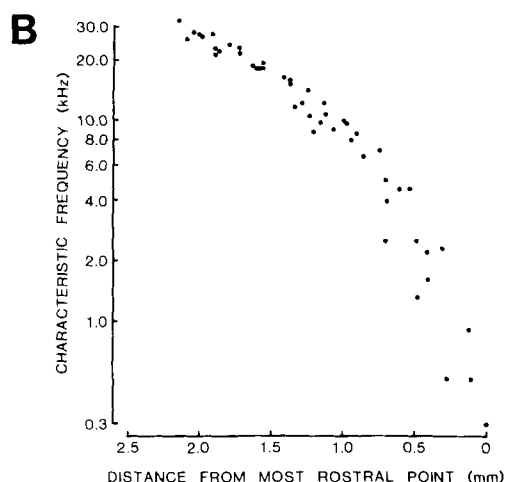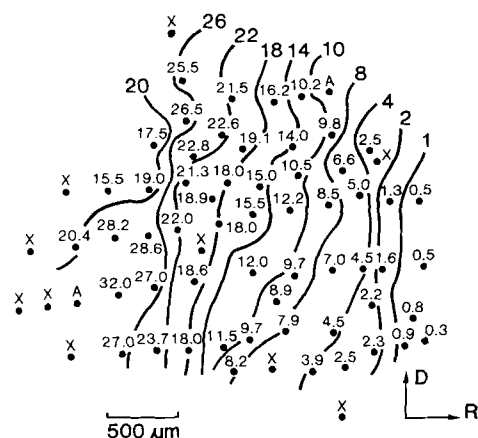
Fig. 2. A: Detailed frequency map of rostral field in a normal animal (animal 86-47, weight 520 g). B: Plot of CF vs. distance for rostral field points only. Conventions as in Figure 1.

Fig. 3. Partial frequency map in normal animal 86-39 (260 g) showing frequency reversal from rostral to caudal field. Broken line marks approximate position of border between fields. Conventions as in Figures 1 and 2.

tral field. The close relationship between CF and cortical locus is indicative of precise tonotopic organization. There is some variability in the distance along the cortex at which a given CF is represented. Some of the factors responsible for such variability, which was seen in all animals, are readily apparent in the frequency map of Figure 1A. In some places, particularly at the dorsorostral edge of the rostral field, considerable compression of the isofrequency lines was apparent in this and some other animals. The irregular trajectories of the isofrequency contours at other points in the field also mean that the contours are parallel only over rather limited distances. Plots of CF vs. distance based on measurements obtained when a single axis is used to determine distance across the entire field do not take account of these characteristics of the isofrequency contours, and these plots consequently often show scatter. In any single line of penetrations along this axis, however, a change of as little as 100 μm in position was always associated with a clear and systematic change in CF.

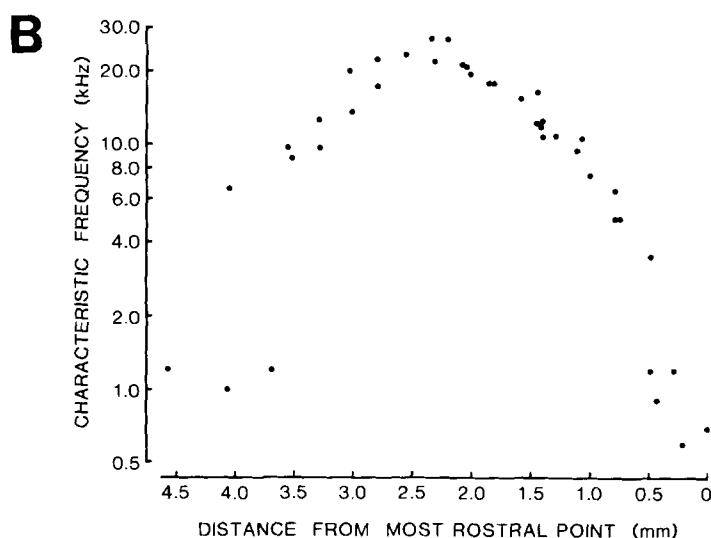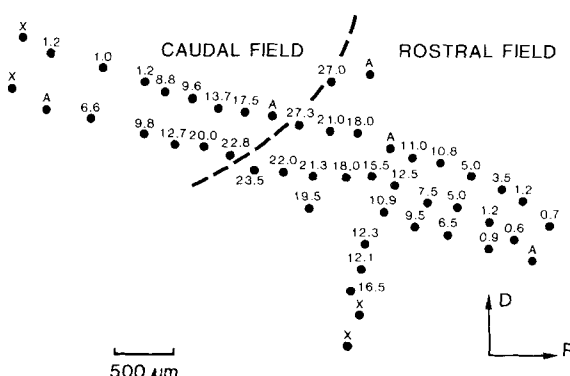An example of a more detailed map largely restricted to the rostral field is presented in Figure 2A,B and shows a similarly precise progression of CF with cortical distance. In Figure 3A, a partial frequency map is presented for an animal in which the frequency reversal from the rostral to the caudal field was shown more clearly by making two to three lines of closely spaced penetrations along the ventrorostral-to-dorsocaudal axis. In the plot of CF against distance in Figure 3B, the rostral field again shows the precise relationship described in the previous cases. The disposition of 1 kHz points in the caudal field in this animal reflects the observation, also made in a number of other cases, that low-frequency contours in the caudal field could be rotated so as to be almost orthogonal to the orientation of isofrequency contours in the rostral field.

Detailed maps showing the essential features illustrated above were obtained in six normal animals, and partial maps showing the same organization were obtained in a further four animals. For eight of these animals, the maximum ros-
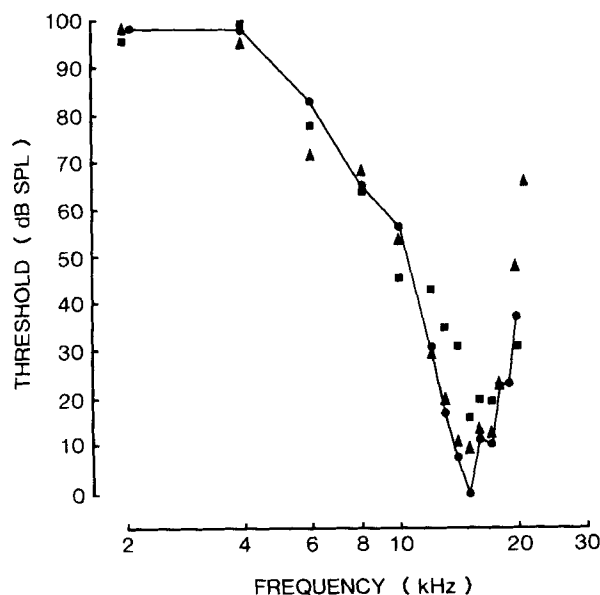
Fig. 4. Examples of normal cluster and single neurone tuning curves measured by using audiovisual criteria at one point in the rostral cortical field of a normal animal. Filled squares and triangles represent the thresholds at a range of frequencies for two clusters recorded at depths of 600 and 750 μm. Filled circles are thresholds and solid line is tuning curve of a single cortical neurone recorded in the same penetration at a depth of 830 μm.

trocaudal extent of the rostral field was measured. This ranged from 1.91 to 2.89 mm (mean = 2.38, S.D. = 0.34 mm). Although the location of the fields relative to the lateral sulcus, their overall shape and size, and the orientation of isofrequency lines varied from animal to animal, a constant feature was the precise relationship between CF and distance across the cortical surface, which was most easily quantified in the rostral field. In view of this and other features, such as its larger size and simpler orientation of isofrequency lines, most attention in this study was focussed on the rostral field. As detailed in the discussion, homologies between these two fields in the guinea pig and the tonotopic fields described in other mammals have not yet been established.

Response characteristics in normal animals

In both the rostral and caudal fields described above, the responses of neurone clusters to pure tone stimuli were typical of those reported in layers III and IV of primary auditory cortex (AI) of other species (Merzenich et al., '75; Reale and Imig, '80; Aitkin et al., '86). In response to stimuli 10 dB or more above threshold, onset responses with latencies in the range of 12 to 20 ms were usually recorded. Clusters at any given location were sharply tuned and CF could usually be assigned with a high degree of accuracy. When cluster responses were obtained at different depths at the same location, they did not differ in CF by more than 0.5 kHz.

In some experiments, audiovisual criteria were used to construct cluster "tuning curves" (threshold vs. frequency response curves). Figure 4 shows two typical examples, together with the tuning curve for a single neurone isolated at the same cortical position. These curves illustrate the
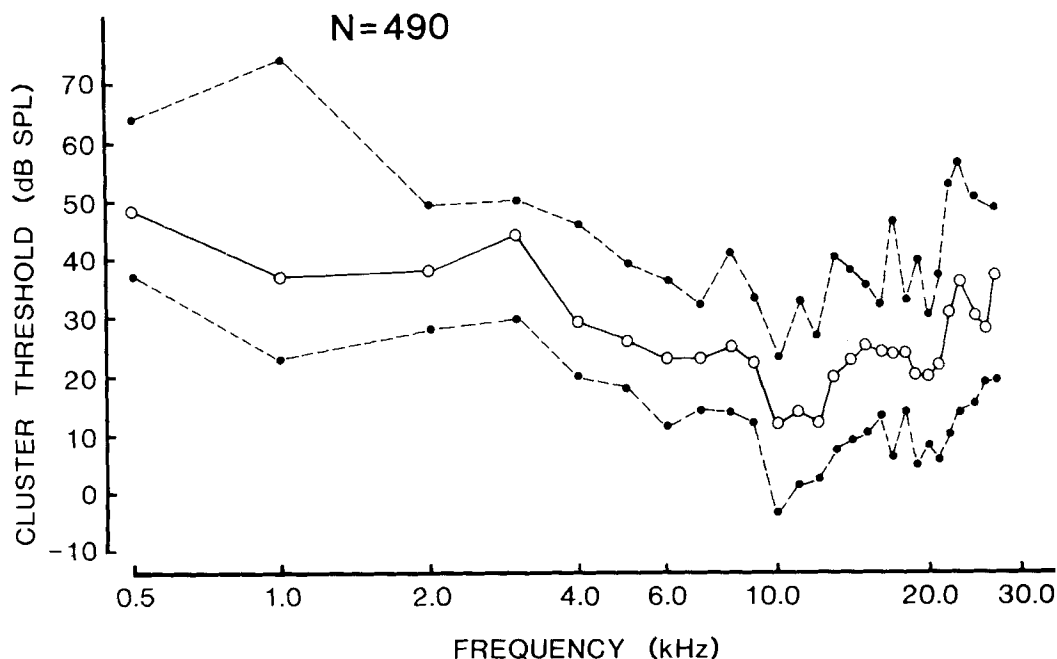

Fig. 5. Mean (open circles; solid line) and range (filled circles; broken line) of thresholds at CF for 490 cortical clusters in ten normal animals. Cluster CFs ranged from 0.5 to 28 kHz. For CFs lower than 23.5 kHz, data have been grouped in 1 kHz bins. Data for CFs between 23.5 and 24.5 kHz were pooled, and data for CFs >27.5 kHz were pooled.
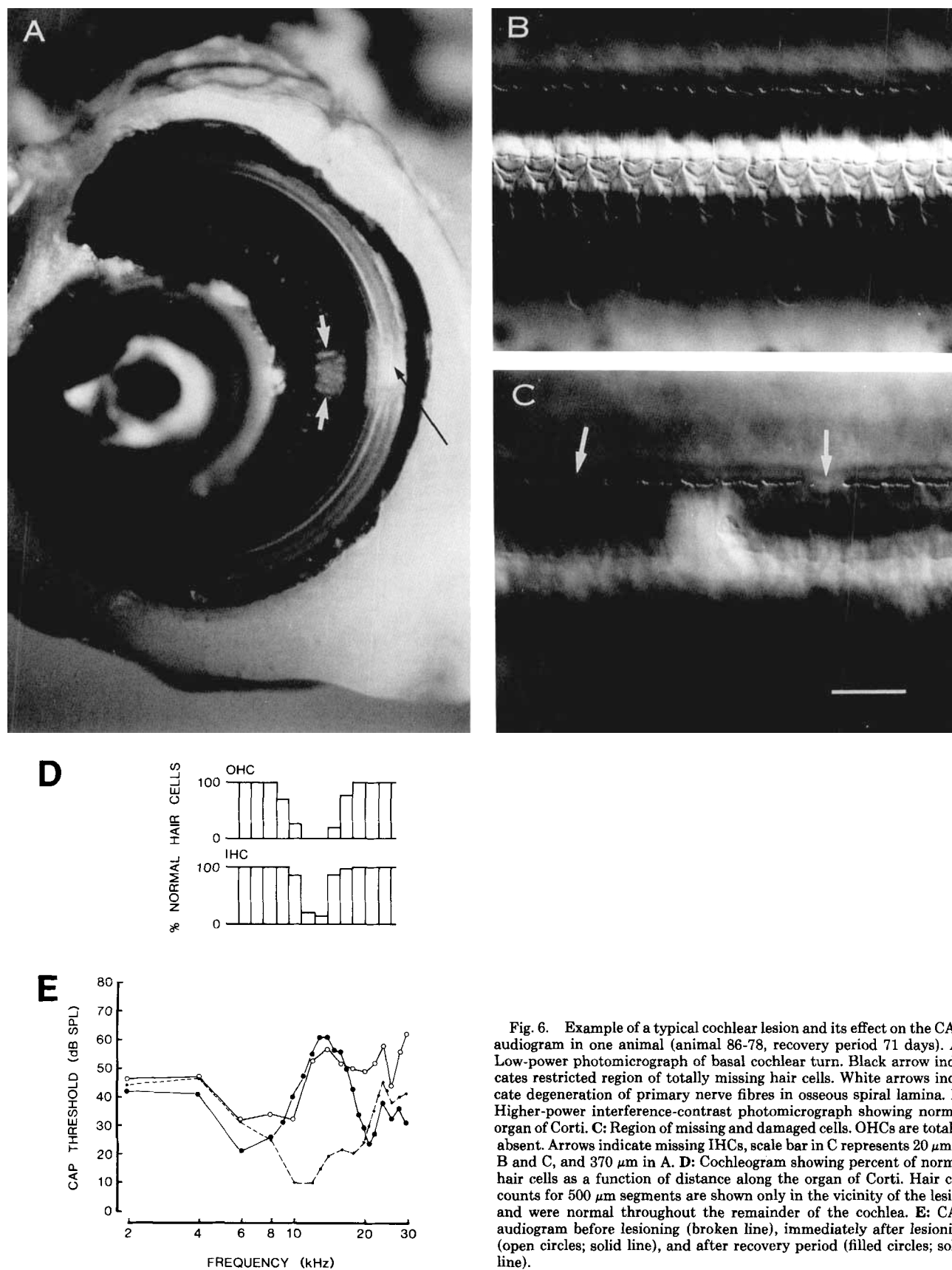
Fig. 6. Example of a typical cochlear lesion and its effect on the CAP audiogram in one animal (animal 86-78, recovery period 71 days). **A:** Low-power photomicrograph of basal cochlear turn. Black arrow indicates restricted region of totally missing hair cells. White arrows indicate degeneration of primary nerve fibres in osseous spiral lamina. **B:** Higher-power interference-contrast photomicrograph showing normal organ of Corti. **C:** Region of missing and damaged cells. OHCs are totally absent. Arrows indicate missing IHCs, scale bar in C represents 20 μm in B and C, and 370 μm in A. **D:** Cochleogram showing percent of normal hair cells as a function of distance along the organ of Corti. Hair cell counts for 500 μm segments are shown only in the vicinity of the lesion and were normal throughout the remainder of the cochlea. **E:** CAP audiogram before lesioning (broken line), immediately after lesioning (open circles; solid line), and after recovery period (filled circles; solid line).
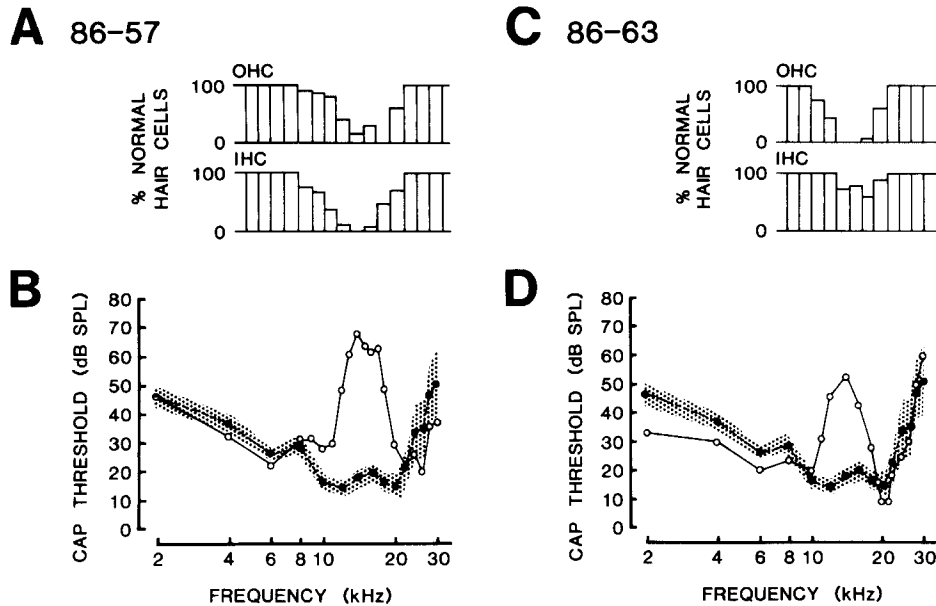
A 86-57

B

C 86-63

D

Fig. 7. Two examples of "notch"-type lesions in animals for which detailed cortical maps were obtained (animals 86-57 and 86-63, recovery periods 35 and 68 days, respectively). A,C: Hair cell counts. B,D: CAP audiograms. In both animals there was mixed IHC and OHC loss and damage. For simplicity, only the postrecovery audiograms are shown for each animal (open circles; solid lines) compared to the mean CAP audiogram for ten normal animals (filled circles; broken line). Shaded areas around normal mean audiogram show 1 S.D.
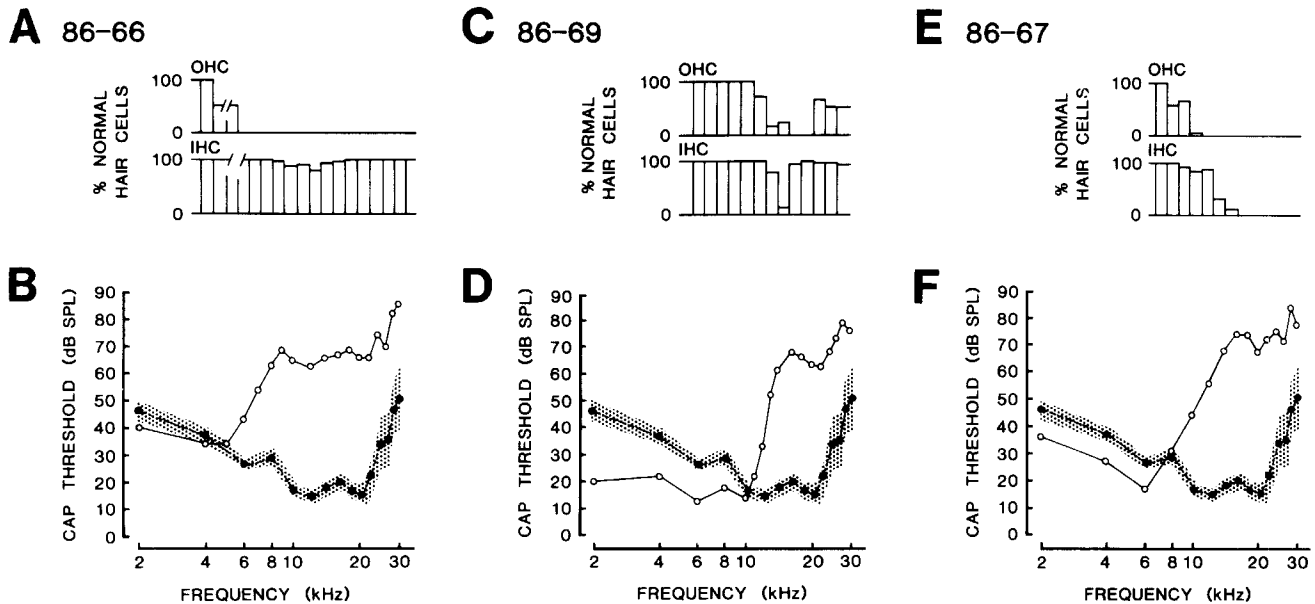

A 86-66

B

C 86-69

D

E 86-67

F

Fig. 8. Hair cell counts (A,C,E) and CAP audiograms (B,D,F) for the three animals with broad high-frequency lesions whose cortical maps are shown below (animals 86-66, 86-67, and 86-69, recovery peri- ods 71, 78, and 81 days, respectively). Details as in Figure 7; discontinuities in hair cell count histograms in A indicate dissection artifact which prevented accurate counting in this region.

sharp tuning of cortical clusters and the constancy of CF at various depths for a given position.

Cluster thresholds at any given CF varied, both across and within animals. Figure 5 shows the mean and range of cluster thresholds in normal animals for CFs ranging from 0.5 to 30 kHz. The overall shape of the mean curve between 2 and 30 kHz agrees reasonably well with the normal CAP audiogram (Figs. 7, 8). The best cluster thresholds are about 10 dB lower than the best thresholds of the CAP audiogram between 2 and 30 kHz.
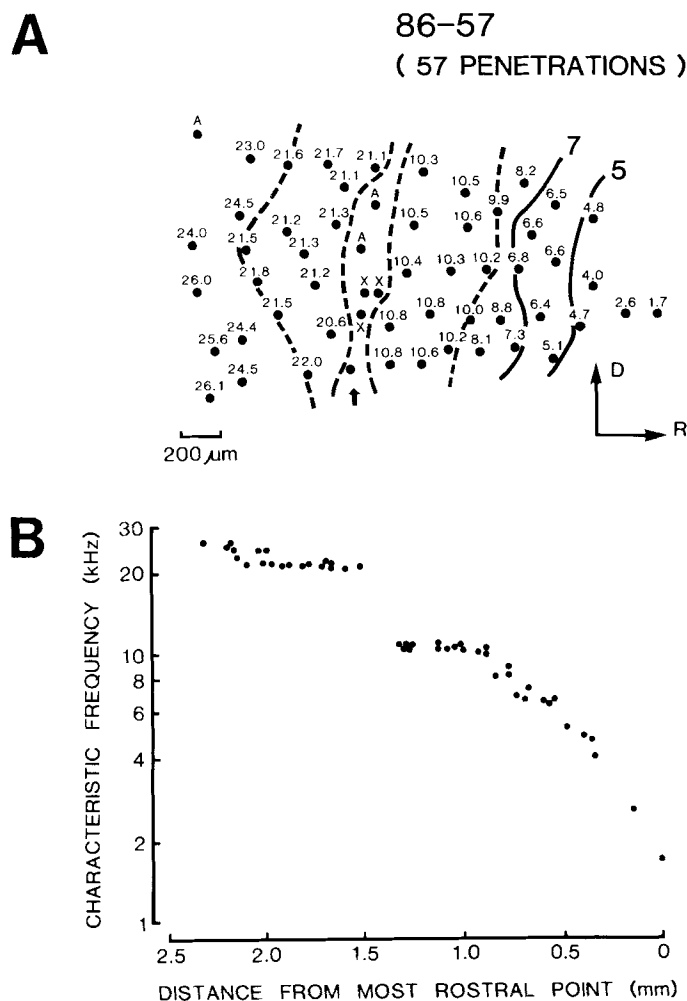
Fig. 9. Cortical frequency map and plot of CF against distance for animal 86-57. Conventions as for previous map displays of cortical data except that broken lines in A delineate areas of expanded frequency representations with sensitive drive. Point marked with arrow in A had equally sensitive responses at 10.6 and 21.4 kHz.
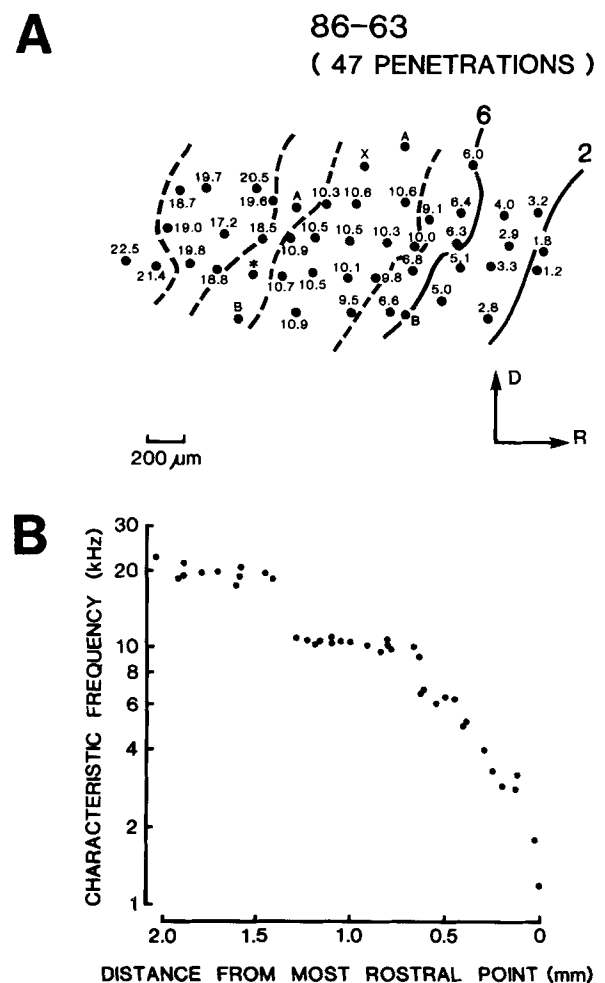
Fig. 10. Cortical frequency map and CF-distance plot for animal 86-63. All conventions as in previous figures. Cluster at point marked B had broad tuning, and cluster at point marked with asterisk responded weakly to both 11 and 18 kHz with approximately equal sensitivity.

Lesion chacteristics

A typical example of the functional and morphological consequences of the lesioning procedure at the level of the cochlea is shown in Figure 6. The prelesion CAP audiogram for this animal is shown in Figure 6E (broken line). The lesioning pipette was advanced into and withdrawn from scala media three times; on the final penetration the pipette was further advanced to penetrate Reissner's membrane (signalled by the sudden disappearance of the endocochlear potential) before withdrawal. The immediate postlesion CAP audiogram (Fig. 6E, open circles) showed a broad loss of sensitivity from 8 to 30 kHz with a peak loss of 43 dB at 12 kHz. After a recovery period of 71 days, the final CAP audiogram (Fig. 6E, filled circles) showed substantial recovery of sensitivity mainly at high frequencies, whilst recovery at the centre of the lesion was negligible. The result was a

"notch" of decreased sensitivity between 9 and 20 kHz, with a peak loss of 45 dB between 12 and 14 kHz.

Associated with this limited frequency band of reduced sensitivity there was a discrete region of the organ of Corti with loss and damage to both inner (IHC) and outer (OHC) hair cells (Fig. 6A–C). Immediately opposite the region of missing and damaged receptor cells, degeneration of the peripheral processes of primary afferent nerve fibres in the osseous spiral lamina was also evident (Fig. 6A). Based on the known place vs. frequency map for the guinea pig cochlea (Robertson et al., '80; Robertson, '84), this lesion of the organ of Corti was at a location along the cochlear spiral which agreed well with the frequency range over which cochlear neural sensitivity was impaired (Fig. 6D,E).

Figures 7 and 8 show the cochlear lesion characteristics and postrecovery CAP audiograms for five animals whose detailed cortical frequency maps will be presented below. The lesions fall into two major classes. Those in Figure 7

show "notch"-type damage similar to that described in the previous example. Nerve fibre degeneration was evident directly opposite the IHC damage in animal 86–57 but was not obvious in animal 86–63.

The cases presented in Figure 8 show more widespread damage to receptor cells associated with a broad high-frequency loss of sensitivity in the CAP audiogram. Two of these examples involved both IHC and OHC loss and damage (Fig. 8C,E), whilst the third (Fig. 8A) showed almost exclusive loss of OHCs, with little significant damage to IHCs. A small region of patchy nerve fibre degeneration was seen opposite the region of IHC damage in 86–69. In animal 86–66, no nerve fibre degeneration was seen. In animal 86–67 there was extensive nerve fibre degeneration beginning at about the 12 kHz location and extending throughout the remaining higher-frequency portion of the cochlea.

Cortical maps in chronically lesioned animals

Results of cortical mapping in the two examples of "notch"-type lesions (animals 86-57 and 86-63; recovery periods of 35 and 68 days, respectively) are shown in Figures 9 and 10. The CAP audiogram of animal 86-57 (Fig. 7B) showed a large loss of sensitivity restricted to the frequency range from 11 to 20 kHz, with marginal losses of CAP sensitivity relative to normal between 8 and 10 kHz. The frequency map of the rostral cortical field in this animal (Fig. 9A,B) is markedly different from those of normal animals. A large region of cortex in which all points have CFs in the range of 9.9 to 10.8 kHz is separated by a narrow strip of poorly responsive cortex from a large region containing CFs in the range of 20.6 to 22.0 kHz. The rostrocaudal extent of these regions is far greater than for the same frequency ranges in normal maps. This is clearly shown by the extended horizontal segments in the plot of CF vs. distance (Fig. 9B). The 9.9–10.8 kHz representation occupies almost 500 μm of cortex compared to less than 100 μm for the same frequency range in normal cortex. The extent of expansion of the 20.6–22.0 kHz representation is similar. The fact that these larger-than-normal representations almost completely occupy the region deprived of its usual input is reflected in the CF vs. distance plot by the small horizontal displacement between the two expanded segments. One point in the map obtained in animal 86-57 (marked by arrow in Fig. 9A) gave low-threshold cluster responses at both 10.6 and 21.4 kHz.

A critical feature of the results from chronically lesioned animals is that neurone clusters in the larger-than-normal representations were strongly driven and that thresholds at most points at the new CFs were similar to those in normal animals. In the case of animal 86-57, the mean threshold in the expanded 10–11 kHz region was only 12.5 dB higher than the mean threshold for all points with CF in that range in normal animals. Although this difference is significant (t = 4.42; $P < .001$), it is in good agreement with the fact that the CAP threshold at 10 kHz was 13dB higher than the mean normal CAP threshold at that frequency. The mean cluster threshold for the expanded 21–22 kHz region in this animal was 4.4 dB lower than normal, a difference which was not statistically significant (t = 1.51; $P > .1$), again emphasizing the apparent normality of the cluster responses in these larger-than-normal representations.

In the second example (animal 86-63), shown in Figure 10, a similar pattern of abnormal cortical representation is seen. In this case, the CAP thresholds were elevated

between 10 and 18 kHz (Fig. 7D). Points with CFs in the range of 9.5 to 10.9 kHz, corresponding to the low-frequency border of the cochlear lesion, occupied about 600 μm in the rostrocaudal axis, indicating an expansion of the representation of this CF range. The mean threshold of clusters in this expanded representation was only 8.1 dB higher than normal (t = 3.41; $P < .01$). Adjacent to this expanded representation there was a small patchy region of poorly responsive cortex and a more caudal region devoted to CFs ranging from 18.5 to 20.5 kHz. Thresholds in this area were close to normal, but the map detail is inadequate to establish whether the latter region is restricted to the rostral field. For this reason, no statistical comparison of thresholds was made.

In both the above examples, there was an absence of points with CFs in the frequency range of the notch in the CAP audiogram. In the small regions of cortex described as poorly responsive, there was either an absence of responsive neurone clusters, or cluster responses were of small amplitude, broadly tuned, and insensitive, and a CF could not be reliably assigned.

In both these examples, the normal progression of CF with distance was found for frequencies below the region of the notch in the CAP audiogram. Whether the very-high-frequency end of the cortical map was normal or not was difficult to assess with certainty because of the considerable compression and scatter seen above about 22 kHz even in normal maps.

Restricted cochlear lesions of this type were produced in five animals, with recovery periods ranging from 35 to 71 days. In four cases, clear abnormalities indicative of expansion of the kind illustrated in Figures 9 and 10 were seen. In the fifth animal, severe cortical pulsation prevented fine grain mapping.

In the three animals in which the cochlear lesion resulted in a broad high-frequency loss of peripheral neural sensitivity, the same basic phenomenon was also seen. In animal 86-69 (Fig. 11A,B), the frequency map appeared normal for low frequencies, although no penetrations were made with CFs lower than 1.5 kHz. The representation of CFs from 9.1 to 10.6 kHz occupied more than 700 μm in the rostrocaudal axis compared with about 100 μm in normal maps. This CF range corresponds closely to the low-frequency edge of the region of reduced sensitivity in the CAP audiogram (Fig. 8D). In this example, seven penetrations were made in the putative caudal field, and it can be seen that there is evidence of similar expansion in this region as well. In this region, the expansion is in the rostral direction from normal, low-frequency caudal points. In the expanded representation, cluster responses appeared qualitatively normal. The mean cluster thresholds were elevated by 6.5 dB relative to normal (t = 3.75; $P < .001$).

In animal 86-66 (Fig. 12), the cortical frequency map showed clear evidence of a larger-than-normal representation of the 5 kHz frequency region, again corresponding closely to the edge of the lesion in the cochlea (Fig. 8B). Points in the area of cortex delineated by the broken lines in Figure 12A all had CFs in the range of 4.9 to 5.4 kHz, and the mean threshold for these points was only 1.9 dB higher than the mean cluster threshold for this frequency range in normal animals. This difference was not statistically significant (t = 1.07; $P > .2$). Caudal to this region there was a large area of cortex in which all but one point had CFs in the range of 5.5 to 6.2 kHz but in which the mean threshold was 31.6 dB higher than the mean threshold for this frequency
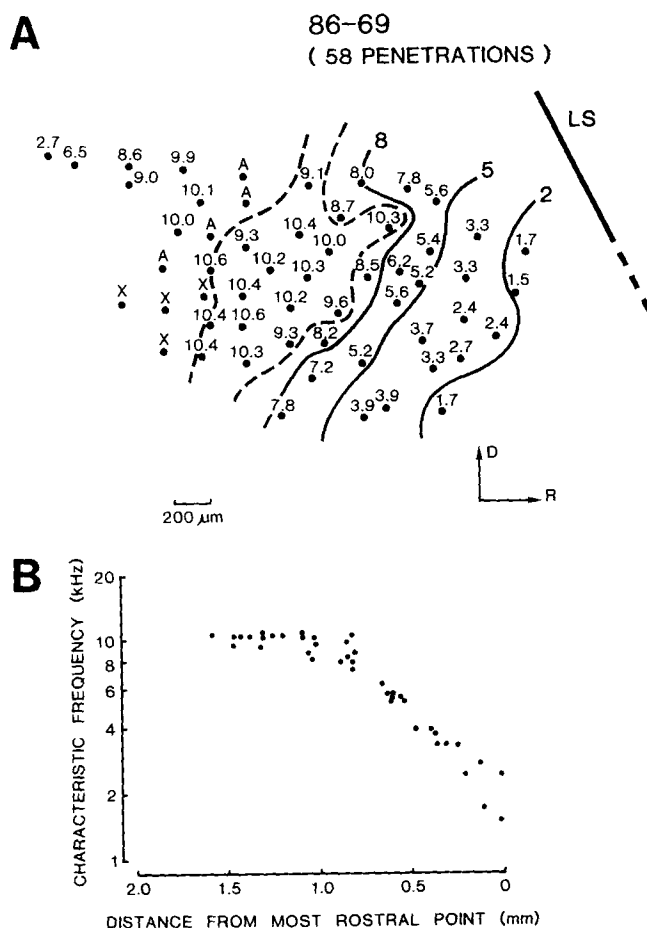
Fig. 11. Cortical frequency map and CF-distance plot for animal 86-69. Seven caudal points at which sensitive cluster responses were obtained are assumed to be located in the modified caudal field. Expansion of the 9–10 kHz representation is apparent here also, but because of the small number of points involved it is not delineated by broken lines. LS, lateral sulcus.
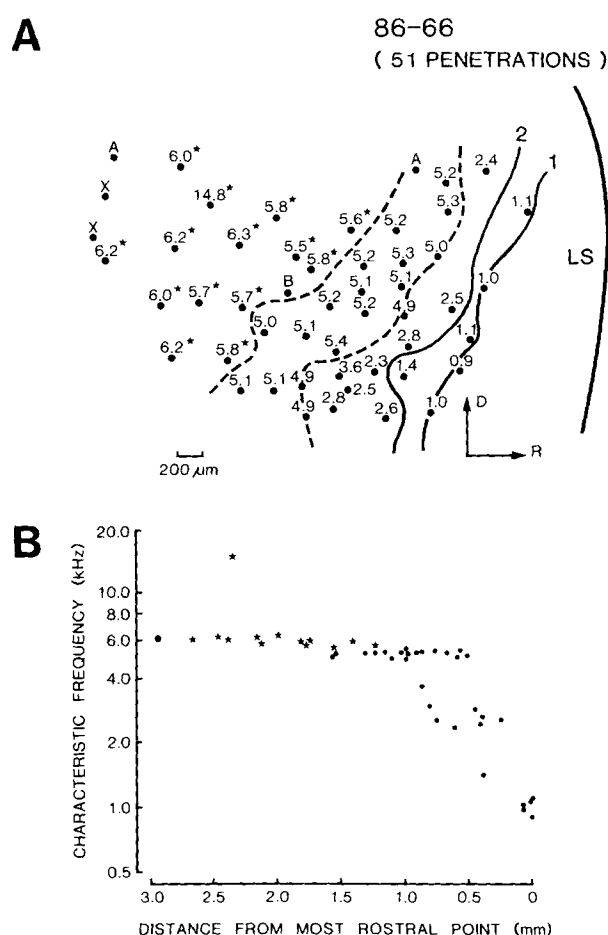
Fig. 12. Cortical frequency map and CF-distance plot for animal 86-66 (postlesion recovery time; 77 days). Points in map at which CF has superscript star are points at which CF could be unequivocally assigned but thresholds were much higher than normal. These points are also indicated by stars in Figure 12B.

range in normals, a difference that was highly significant (t = 13.45; P < .001). This was the only animal showing such an extensive region of reduced sensitivity in addition to the expanded region of near-normal sensitivity. The cochlear lesion in this animal (Fig. 8A,B) was also unusual in that the damage was confined almost exclusively to the OHCs. The CF vs. distance plot in this animal showed considerable scatter at low frequencies (Fig. 12B). This was the result of irregularities in the 2–3 kHz isofrequency contours particularly near the ventral edge of the field and did not appear to reflect a breakdown in normal tonotopic organization at these frequencies.

Figure 13 shows a further case in which there was significant expansion of the representation of the 6–7 kHz frequency range, in conformity with the low-frequency edge of the cochlear lesion. The cochlear lesion (Fig. 8E) resulted in loss of both IHCs and OHCs with a total absence of sensory cells and extensive nerve fibre degeneration above 15 kHz. Only a partial map was obtained in this case because of the premature death of the animal. The mean threshold for the points in the expanded frequency representation was 4.8 dB

more sensitive than normal, a difference which was statistically significant (t = 2.08; P < .05).

Across all the above cases in which the expansion of sensitive drive could be quantified (N = 7 in six animals) the mean difference between cluster thresholds in the expanded sensitive regions of cortex (i.e., excluding the high-threshold points in animal 86-66; Fig. 12) and those for points of the same CF in normal animals was only 3.8 dB. This difference was not significant (t = 1.53; P > .01).

Cortical maps in acutely lesioned animals

In a second group of five animals (630–840 g), partial cortical frequency maps were obtained within the first few hours, rather than weeks, after lesions to the sensory epithelium. In these animals the postlesion maps showed no evidence of an expanded region of low-threshold responsiveness. Rather, points whose prelesion CF fell within the frequency range of the lesion often had CFs at adjacent unaffected frequencies, but the thresholds of clusters were greatly elevated with respect to normal.
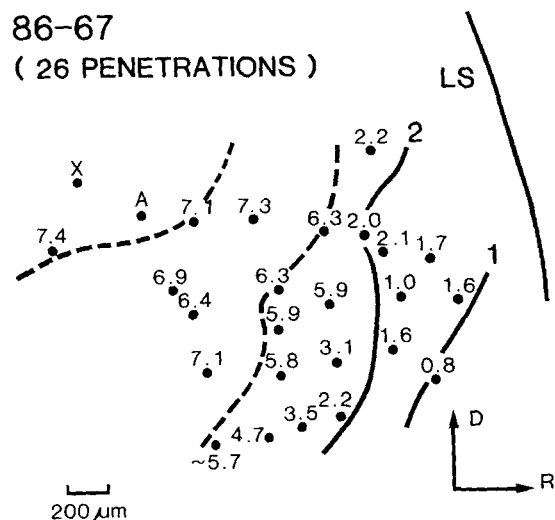
Fig. 13. Partial cortical map obtained for animal 86-67. Because of the small number of penetrations, no plot of CF vs. distance is shown, but the 6–7 kHz zone appears to occupy a maximum rostrocaudal distance of about 700 μm. Point marked by number preceded by tilde (~) was broadly tuned and CF could only be approximately assigned. Other details as in previous figures.
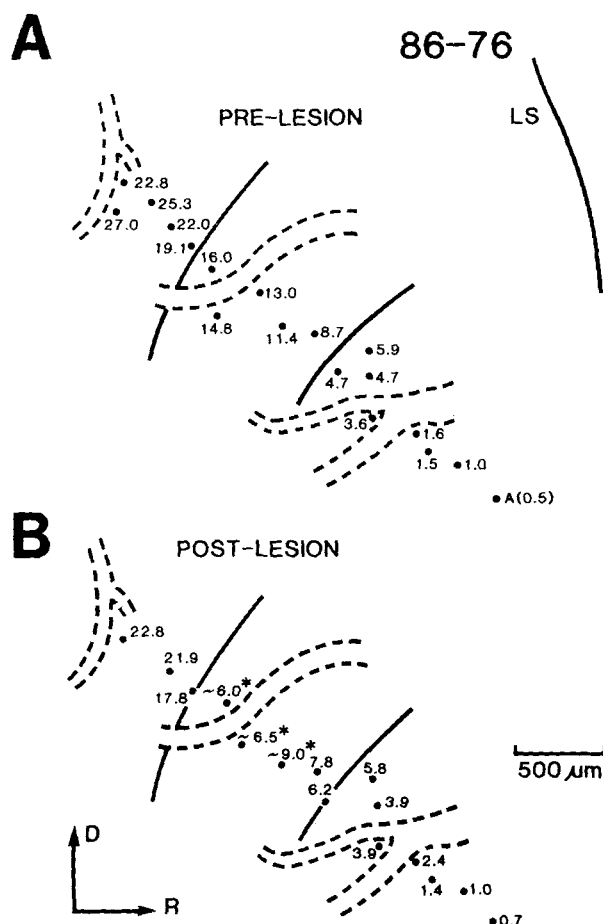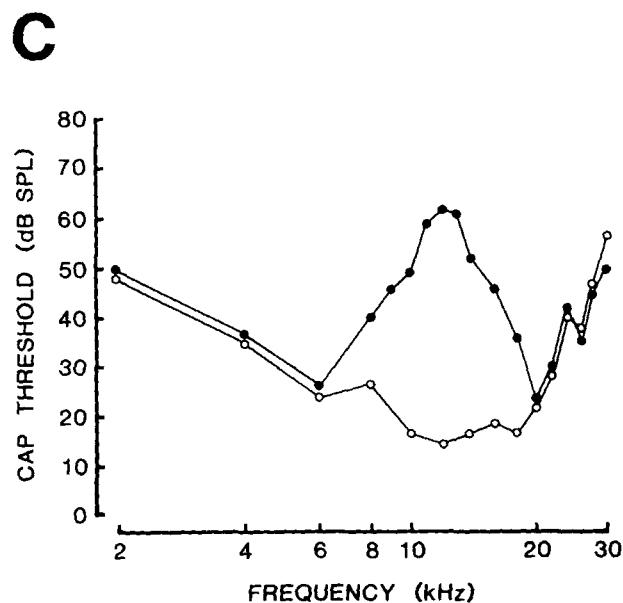

Fig. 14. Partial cortical frequency maps in an acute lesioning experiment (animal 86-76). A: CFs in a line of penetrations across cortical surface before lesioning. Broken lines show outlines of major cortical blood vessels in the mapped area. B: CFs obtained within about 5 hours of making cochlea lesion at points as close as possible to those at which

Results from one such animal are shown in Figure 14. After initially establishing that the CAP audiogram was normal (Fig. 14C; open circles), a single line of penetrations was made across the cortical surface in the rostral field and CFs of cortical clusters were determined at each point. A lesion was then made in the cochlea so as to produce a loss of sensitivity in the CAP audiogram similar to the "notch"-type lesions described in Figures 7 and 8 (see postlesion CAP audiogram in Fig. 14C; filled circles). A second series of penetrations was then made as close as possible to the initial points on the cortex, and the CF and thresholds of clusters were again measured. In most cases penetrations were able to be made at almost exactly the same loci, but in some instances bleeding from the original penetration meant that the postlesion recording had to be made at an immediately adjacent locus.

There was good agreement between pre- and postlesion CFs for all points outside the region of elevated CAP threshold. However, most points whose prelesion CFs fell within the lesioned frequency range had greatly elevated thresholds at their original CFs. The new CFs of clusters at these points were either higher or lower in frequency than before the lesion, tending to correspond to the boundaries of the lesion as defined by the CAP audiogram. The greatest shift of CF seen was from 16 kHz to approximately 6 kHz. These points were often broadly tuned and their CFs were some-

prelesion CF determinations were made. Other details as in previous figures. C: CAP audiograms before (open circles) and immediately after (closed circles) making the lesion in the cochlea. Solid lines in A and B denote the approximate rostral and caudal limits of within-lesion cortex based on the changes in the CAP audiogram.
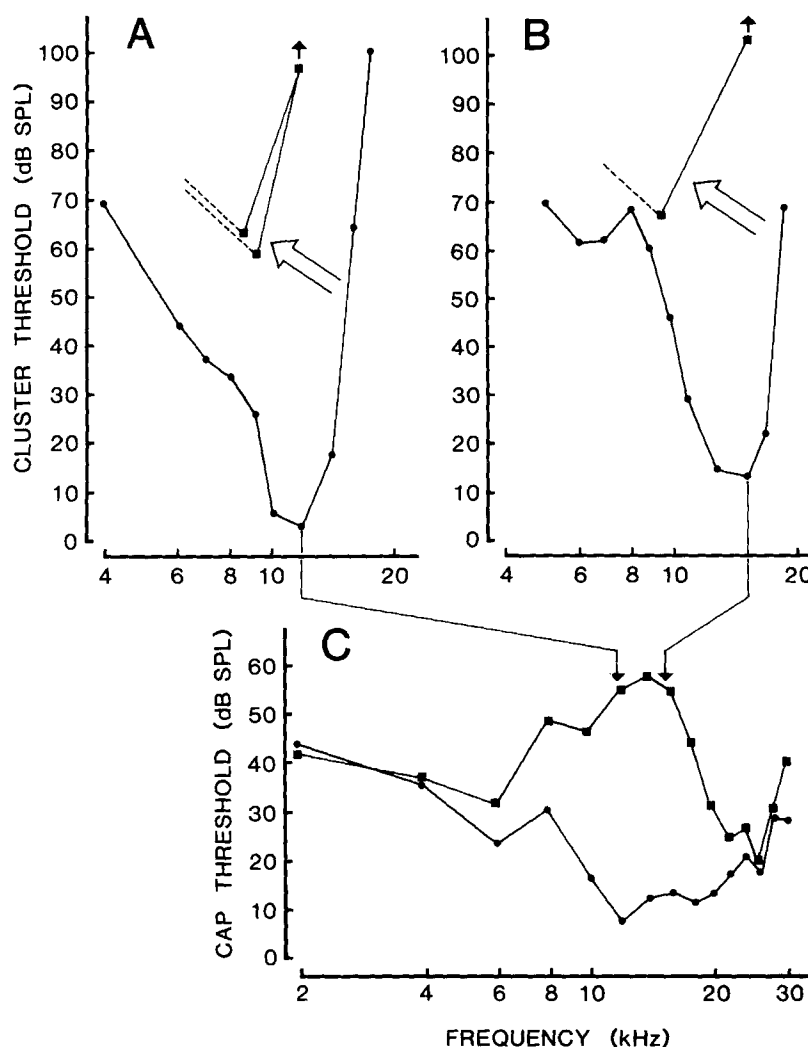
Fig. 15. Results of measurements of cluster thresholds at a range of frequencies (cluster tuning curves) at two cortical penetration sites before and immediately after a cochlear lesion (animal 87-5). Clusters were recorded at the same two cortical loci before and after lesioning. A,B: Cluster tuning curves before lesioning (filled circles) and thresholds at old and new CFs (filled squares). Prelesion CFs were 11.8 and 15.2 kHz, respectively. At the same points, postlesion CFs were 8.7 and 9.3 kHz for two clusters in A and 9.5 kHz for one cluster in B. Small vertical arrows on threshold points indicate that clusters did not respond at the maximum sound pressure of 100 dB. C: CAP audiogram before (filled circles) and after (filled squares) cochlear lesioning. Arrows connecting A and B with the CAP audiogram in C indicate that both clusters have original CFs which fall within the frequency range most affected by the cochlear lesion.

times difficult to define. Furthermore, the thresholds of these within-lesion clusters at their new CFs were greatly elevated relative to normal cluster thresholds at the new CFs. The mean cluster threshold for within-lesion points whose CFs ranged from 6.0 to 9.0 kHz was 31.7 dB higher than the mean of normal cluster thresholds in this frequency range (t = 8.5; $P < .001$).

This basic result of a shift in cluster CFs with greatly elevated thresholds was found in all five acute-lesion experiments. Two within-lesion points were so insensitive, and the clusters so small and broadly tuned, that they could not be characterized accurately. Across the five animals, the mean threshold at the postlesion CF for all within-lesion points

was 31.6 dB higher than the mean thresholds for points of the same CF in normal animals, and this difference was highly significant (t = 5.91; $P < .005$).

In two of the five animals cluster tuning curves were measured at several points before the lesion was made. Figure 15A,B shows such curves from one animal, together with the sensitivity of clusters at the new and original CFs for two within-lesion points. The elevation of threshold at the original CF was more than 80 dB in both cases. The thresholds of clusters at their new CF clearly fell within the response area of the prelesion tuning curves at these points (Fig. 15A,B), and these thresholds at the new CF were greatly elevated when compared to the normal thresholds of clusters with CF

at these frequencies. Thus, these results provide no evidence for the sudden emergence of sensitive responses at new CFs immediately after lesioning the peripheral receptor.

DISCUSSION

It is apparent from these results that, following restricted damage to the cochlea, there is significant reorganization of the topographic representation of sound frequency in the adult auditory cortex. Immediately after such damage, neurones in the region of cortex in which the damaged part of the cochlea is normally represented often have CFs shifted toward frequencies outside the range of the lesion, but their thresholds are grossly elevated relative to the normal thresholds of neurone clusters with CF at these frequencies. Subsequently, neurones in at least part of this deprived region develop near-normal thresholds with CFs at frequencies near those represented at the edges of the damaged region. This result, together with the complete absence (except for one point in animal 86-66) of points with CFs in the frequency range of the peripheral lesion, strongly suggests that there has been an expansion of the representation of the frequencies at the low- and high-frequency borders of the lesion. This progressive emergence of new low-threshold representations in the cortical frequency map appears to be closely analogous to changes reported in cortical somatotopic maps after peripheral nerve section in adult primates (e.g., Merzenich et al., '83a,b). These data raise a number of issues which will be examined in the following sections.

Time of occurrence and time course of reorganization

The mean weight of chronically lesioned animals at the time of cochlear lesion was 317 g (about 5 weeks postnatal age), and their mean weight at the time of final cortical mapping was 661 g (about 12 weeks postnatal age). The cortical frequency maps from normal animals of weights ranging from 260 to 730 g showed no differences in the organization of either rostral or caudal fields. The changes seen postlesion are therefore undoubtedly caused by the lesion and not by developmental progressions in the organization of the maps, which would have occurred in the absence of lesioning. It is still possible that the age of the animals at the time of the lesion may have a bearing on the ability of the cortex to respond to deprivation of input in the manner we have described. We believe this is not a factor in our experiments, since all animals in which adequate postlesion maps could be obtained showed clear evidence of expanded representations of frequencies at the edge of the lesion, regardless of their weight at the time of lesioning. Furthermore, the extreme precocity of the guinea pig (see Harper, '76, for review) makes it unlikely that the lesions fell within some critical period of postnatal development. We therefore feel confident that the changes we have described are a property of adult auditory cortex.

The detailed time course of these changes was not investigated, since multiple mapping experiments over many days in the one animal were not performed. Evidence for reorganization of the cortical frequency map was obtained as early as 35 days and as late as 81 days after the lesion to the receptor epithelium. In the five animals in which cluster CFs and thresholds were measured immediately postlesion, all points which fell clearly within the frequency range of the cochlear lesion had grossly elevated thresholds, whether they were measured within minutes or hours of lesioning the

cochlea. The maximum duration of these acute experiments was 10 hours and we cannot say when between this time and 35 days the emergence of expanded sensitive representations becomes apparent. The present results may be compared with the time course of changes reported in somatosensory cortex. In the rat's cortex, reorganization has been reported to be detectable 24 hours after partial deafferentation (Wall and Cusick, '84), whilst in primate somatosensory cortex, after median nerve section, major expansions of neighbouring representations become apparent 22 days postlesion (Merzenich et al., '83a). Whether such differences reflect species variation or different methodologies is not clear.

Locus of reorganization

We generally restricted frequency mapping in chronically and acutely lesioned animals to the rostral cortical field because of its larger size and simpler frequency organization. In the few chronic animals in which observations were made in the caudal field, the limited data suggested that the same type of frequency reorganization had also taken place there (e.g., animal 86-69; Fig. 11). It therefore seems likely that similar plasticity is characteristic of both of the tonotopically organized cortical fields we have described in the guinea pig. It is unfortunately not known which of these fields is the homologue of primary auditory cortex (area AI) as described in other mammals. In most mammals in which the organization of auditory cortex has been described in detail, AI is bordered rostrally by a tonotopically organized field with mirror-image frequency organization, commonly termed the anterior auditory field (AAF or field A in the cat; see Aitkin et al., '84; Brugge and Reale, '85, for reviews). Although this might suggest that the caudal field in the guinea pig is homologous to AI, the definition of AI as the primary field is based not on relative position but on cytoarchitectonic criteria and on the pattern of thalamocortical projections to the various fields. There has been no description of the cytoarchitecture of physiologically defined auditory cortical fields in the guinea pig, and the available evidence on the thalamocortical connections of the rostral and caudal fields (Redies and Creutzfeldt, '87) does not resolve the question of which is to be identified as AI.

The fact that we have observed changes in the frequency organization of the tonotopic fields in auditory cortex does not, of course, mean that the primary locus of such plasticity is the cortex. The possibility should be considered that the changes seen in cortical reorganization are merely a reflection of changes occurring at lower stages in the ascending pathway. In the somatosensory system, reorganization after peripheral nerve lesion and blockade have been reported at the level of the brainstem and spinal cord (Millar et al., '76; Dostrovsky et al., '76; Basbaum and Wall, '76; Merrill and Wall, '78; Devor and Wall, '78, '81a,b). There is some preliminary evidence to suggest that reorganization of frequency maps occurs in the inferior colliculus of adult guinea pigs after cochlear lesions similar to those reported in the present study (Robertson and Winter, unpublished observations).

Possible mechanisms underlying observed changes

In considering possible mechanisms, the nature of the peripheral lesion needs to be taken into account. In contrast to the somatosensory system, it is not possible with present techniques reliably to produce complete deafferentation in

a restricted region of the cochlea nor to specify at will the extent and details of hair cell damage. The character of the cochlear lesions therefore varied considerably. Some of the lesions involved substantial degeneration of primary nerve fibres and others did not. Most involved mixed IHC and OHC damage whilst one involved only destruction of OHCs. In some cases all receptor cells were destroyed in a limited region; in others, intact receptors were still present in substantial numbers even in the anatomical centre of the lesion.

In view of all these confounding factors, what is striking is the highly consistent nature of the changes seen in the cortical frequency map after recovery periods of 35 days or more. In all cases in which reliable maps were obtained, a clear expansion of neighbouring frequency representation was observed which could not be accounted for either by experimental error or by residual drive remaining immediately after such lesions were made. The simplest explanation is that a sufficient loss of peripheral sensitivity, regardless of its precise cause, will trigger the reorganization. Certain features of the results suggest that the amount of peripheral sensitivity loss may be important in determining whether a given frequency region in the cortex is taken over by neighbouring frequency representations or whether it can itself take over other adjacent regions which have suffered a greater loss of input. For example in animal 86-57, although the CAP audiogram showed a loss of about 13 dB at 10–11 kHz, this frequency range showed a clear expansion in its cortical representation, encroaching on regions in which the peripheral sensitivity change was greater.

When the mechanism underlying such plasticity is considered, two fundamental questions have to be addressed. Firstly, what is the nature of the residual high-threshold responses seen immediately after desensitizing lesions to the cochlea? Secondly, one can ask what changes occur to convert the high-threshold residual responses into the secure low-threshold responses at frequencies at the edge of the lesion that are seen in the expanded representations after the recovery period.

A consideration of the nature of the immediate postlesion residual responses is complicated by the fact that in the case of incomplete lesions to the receptor surface there is undoubtedly substantial residual afferent drive, albeit high threshold, emanating from the lesioned regions of the peripheral receptor. This residual primary afferent drive is known to be altered in its frequency selectivity. When the function of the OHCs is impaired, primary afferent fibres emanating from the damaged regions lose the sharp sensitive tips to their tuning curves and have broad insensitive tuning curves with high-frequency cutoffs shifted to lower frequencies (Robertson and Johnstone, '79; Liberman, '84; Liberman and Dodds, '84). Thus, the high-threshold lower-frequency responses often seen at within-lesion points in auditory cortex immediately after cochlear lesions probably represent remaining drive from the damaged cochlear regions which has shifted its CF, rather than drive from the lower-frequency regions of the cochlea. Indeed, the results shown in Figure 15 are quite reminiscent of the changes seen in primary afferent nerve fibres after impairment of receptor cell function. Despite the difficulty in interpreting the normal cluster tuning curves, those shown in Figures 4 and 15 clearly illustrate that there is substantial, though less sensitive, drive at frequencies well removed from CF at a given point in the normal auditory cortex. When combined with the fact that residual high-threshold primary afferent

responses at frequencies lower than the original CF can often be present in cochlear regions sustaining hair cell damage without total deafferentation, the residual responses seen in the cortex are most simply explained as a vestige of responses normally present. In the somatosensory system, mechanisms such as "unmasking" or "disinhibition" have been invoked to explain the rapid emergence of new receptive field boundaries after deafferentation, both at the cortical (Metzlar and Marks, '79; Calford and Tweedale, '88) and subcortical level (Dostrovsky et al., '76). It seems unecessary to invoke such mechanisms to explain the high-threshold responses remaining in the auditory cortex immediately postlesion in the present experiments.

The most plausible explanation for the subsequent expansion of neighbouring CF representations with secure low-threshold responses would seem to be that input from other regions of the cochlea, which is normally fairly ineffective, becomes more effective during the recovery period.

There would appear to be limits to the extent of cortex over which this change can occur. The upper limit in our experiments would appear to be about 700 μm in the rostro-caudal axis, a figure which agrees fairly well with some reports in somatosensory cortex (Merzenich et al., '84). In the one animal (86-66) with a pure OHC lesion (Fig. 8A) the cortex not only contained the region of expanded sensitive drive seen in all lesioned animals after recovery, but also a large area responding to the edge frequency, but with elevated threshold (Fig. 12). This lesion was similar to the widespread OHC lesions produced by prolonged courses of kanamycin (Robertson and Johnstone, '79). The residual primary afferent drive from the damaged cochlear region could well form the basis for the extensive region of high-threshold, broadly tuned responses seen in the cortex of this animal outside the area in which expansion of sensitive drive had occurred.

Expansions of cortical representations in the adult somatosensory system have been postulated to reflect changes in the effectiveness of synapses within preexisting thalamocortical terminal arbors (Kaas et al., '83; Jenkins and Merzenich, '87; Pearson et al., '87) rather than a physical sprouting of terminations. Such arborizations, in this and other sensory systems, are thought to be anatomically far more extensive than the physiologically measured receptive fields would predict (Scheibel and Scheibel, '70; Wall, '77; Ferster and LeVay, '78; Pons et al., '81; Blasdel and Lund, '83), and a given point on the cortical surface has the potential at least to receive input from other parts of the receptor surface if the normal dominant drive is removed. The limit of about 700 μm observed for the expansion in area 3b of primate somatosensory cortex has been postulated to reflect the physical limits of convergence of subcortical inputs to a given cortical site (Merzenich et al., '84).

There is still, however, considerable conjecture as to the nature of the changes that render these inputs progressively more effective during reorganization. There could, for instance, be an increase in the effectiveness of preexisting synapses or a proliferation of new synaptic contacts on cortical neurones (see Cotman et al., '82, for review) within the boundaries of the existing terminal arborization. Nor is it known with certainty what mechanisms normally regulate the effectiveness of cortical synapses, or how changes of input affect these mechanisms so as to give rise to the altered representations. A recent report (Clark et al., '88) provides some evidence for the notion that the normal boundaries of body-part representations in somatosensory

cortex are maintained by the temporal coherence of excitation of primary afferents innervating neighbouring body parts. Similar mechanisms could conceivably operate in the auditory system. The physical nature of the travelling wave which underlies the segregation of sound frequency along the length of the cochlea (see Patuzzi and Robertson, '88, for review) means that there should be a systematic tendency for inputs to the central nervous system from adjacent cochlear regions to be correlated in time.

Whatever the mechanism/s are, the present results suggest that the potential for reorganization may be an inherent property of sensory systems in general. The type of damage to the cochlea in this study is very similar to that found in humans after many types of ototoxic insults and age-related degeneration (Bredberg, '68). It is therefore possible that in many instances of partial deafness in humans, similar alterations of auditory cortical organization occur. The consequences of such reorganization for the processing of auditory information have not as yet been investigated.

ACKNOWLEDGMENTS

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