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# Auditory activation of 'visual' cortical areas in the blind mole rat (*Spalax ehrenbergi*)

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## Abstract

The mole rat (*Spalax ehrenbergi*) is a subterranean rodent whose adaptations to its fossorial life include an extremely reduced peripheral visual system and an auditory system suited for the perception of vibratory stimuli. We have previously shown that in this blind rodent the dorsal lateral geniculate nucleus, the primary visual thalamic nucleus of sighted mammals, is activated by auditory stimuli. In this report we focus on the manifestation of this cross-modal compensation at the cortical level. Cyto- and myeloarchitectural analyses of the occipital area showed that despite the almost total blindness of the mole rat this area has retained the organization of a typical mammalian primary visual cortex. Application of the metabolic marker 2-deoxyglucose and electrophysiological recording of evoked field potentials and single-unit activity disclosed that a considerable part of this area is activated by auditory stimuli. Previous neuronal tracing studies had revealed the origin of the bulk of this auditory input to be the dorsal lateral geniculate nucleus which itself receives auditory input from the inferior colliculus.

## Introduction

Amongst other major adaptations to its dark subterranean environment, the mole rat has a visual system extremely reduced in size. The diameter of the adult's eyes, which are covered by skin and fur, is 0.6–1.0 mm (Bronchti *et al*., 1991b; Herbin *et al*., 1995; David-Gray *et al*., 1998), much smaller than the average 6.3 mm of the pigmented rat's eye (Herbin *et al*., 1995). Lens, iris and ciliary body are largely degenerated (Cei, 1946; Leder, 1975; de Jong *et al*., 1990; Herbin *et al*., 1995) but there is a well-defined retina whose receptor cells contain a long-wavelength sensitive photopigment with an absorption maximum of 534 nm, one of the most 'red-shifted' cone photopigments identified in rodents (David-Gray *et al*., 1998).The optic nerve in the adult consists of ≈1000 unmyelinated axons, <1% of the number of myelinated fibres found in the rat's optic nerve (BreMiller *et al*., 1986; Herbin *et al*., 1995; our own unpublished observations), most of these terminating in the suprachiasmatic nucleus (Bronchti *et al*., 1991b; Cooper *et al*., 1993a; Cooper *et al*., 1993b). Few optic fibres reach the thin superficial layers of the superior colliculus, the optic tract nucleus or the ventral lateral geniculate body (Bronchti *et al*., 1991b; Cooper *et al*., 1993a; Cooper *et al*., 1993b). These retinofugal projections most probably mediate the animal's sensitivity to light (Leder, 1975; Rado *et al*., 1992b) and provide the neuroanatomical basis underlying its circadian activity (Rado *et al*., 1988; Rado *et al*., 1992a; David-Gray *et al*., 1998). In newborn mole rats, some retinofugal fibres enter the dorsal lateral geniculate body (dLGB), the main thalamic visual nucleus in sighted mammals. However, most of these projections degenerate within the first weeks of life (Bronchti *et al*., 1991b), due to a reduction in the number of retinofugal axons by >90% (compared to ≈50% in seeing rodents): the optic nerve of the newborn is composed of ≈12000 unmyelinated axons, ≈12 times as many as in the adult (our unpublished observations). In the adult mole rat, Cooper *et al*. (1993b) found a few retinal fibres terminating in a small structure which they, and Rehkämper *et al*. (1994), consider to be the entire dLGB. Even though some of its cells project to a visual cortex, as they can be retrogradely labelled by injections of tracer into the ipsilateral occipital cortex (Cooper *et al*., 1993b), it has been impossible to record visual evoked potentials in the occipital cortex (Haim *et al*., 1983; Necker *et al*., 1992; our own unpublished observation). Thus, in spite of its sensitivity to light, the mole rat can be considered functionally blind.

For mole rats, the auditory system plays a significant role in both social and survival behaviours. Vocalizations are used for short-distance communication between mother and pups or between adults when they meet during the mating season (Capranica *et al*., 1974; Nevo *et al*., 1987; Rado *et al*., 1991). Except during these circumstances, mole rats are solitary and each individual excavates its own tunnel system. To avoid potentially fatal physical encounters with conspecifics outside the mating season and to enable contacts between males and females for mating, long-distance communication between individuals inhabiting different tunnel systems is necessary. For this purpose, mole rats use patterned vibratory (seismic) signals that they produce by tapping the head against the roof of the tunnel (Heth *et al*., 1987; Rado *et al*., 1987). The signals are perceived by the receiver pressing its lower jaw against the tunnel wall, and are transmitted to the inner ear by means of bone conduction (Rado *et al*.,

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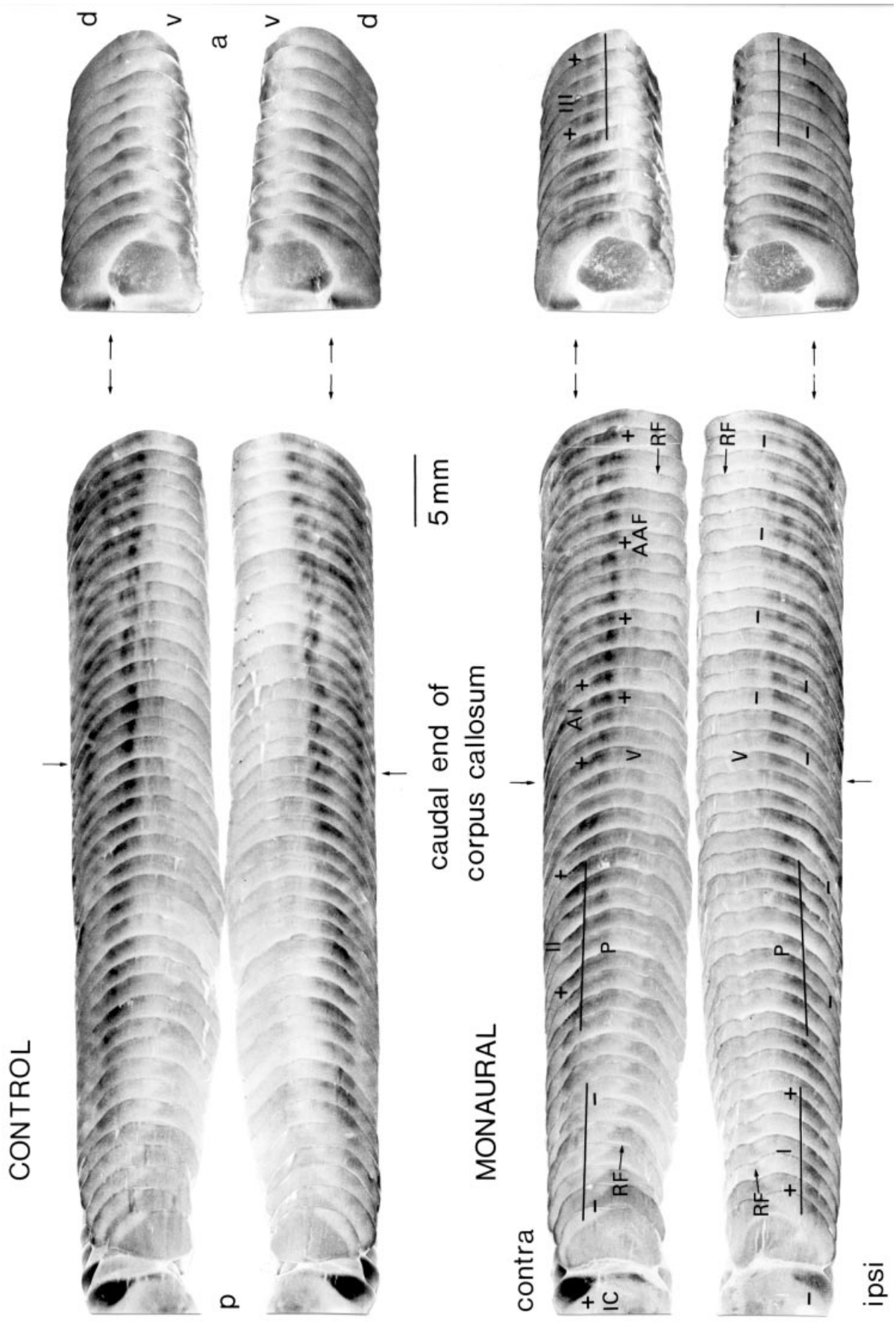



FIG. 1. Overview of cortical 2DG patterns in a noise-stimulated (top) intact (control) mole rat and (bottom) a unilaterally deafened (monaural) case. The montages were prepared as follows: photographs of autoradiograms from transverse sections were cut out and then cut along the midline of the brain. Each hemisection was rotated by 90° in opposite directions so that the ventral surfaces face each other. Hemisections were then mounted from anterior (a; right) to posterior levels (p; left) such that all but the cortical hemisphere of the more rostral hemisection is covered by the adjacent more caudal hemisection. The average interval between sections is 160 μm. Note that the anteroposterior axis appears stretched relative to the dorsoventral one. The gaps in the hemisection montages represent ≈ 3 mm along the anteroposterior axes of the brains without structures of interest for this study. The horizontal arrows in the gaps indicate the dorsal margin of the corpus striatum and the vertical arrows above and below each montage the splenium of the corpus callosum. Stronger and weaker 2DG uptake in a comparison of the two hemispheres in the monaural animal are identified by + and −, respectively. Abbreviations: AAF, anterior auditory field; AI, primary auditory field; P, posterior auditory field; V, ventral auditory field; RF, rhinal fissure; IC, inferior colliculus; I, II, III, cortical areas I, II, and III; a, anterior; p, posterior; d, dorsal; v, ventral. Note the asymmetric 2DG labelling in IC and cortex of the monaural case.

1989; Rado *et al*., 1998). They are then processed by the auditory system, as strongly suggested by behavioural observations and electrophysiological measurements (Wollberg *et al*., 1997; Rado *et al*., 1998). The vibratory signals consist of low-frequency components (Heth *et al*., 1987; Rado *et al*., 1987) which correspond with the hearing apparatus and hearing sensitivity of the mole rat (Burda *et al*., 1988; Bronchti *et al*., 1989; Heffner & Heffner, 1992) as well as with the transmission properties of the underground habitat (Heth *et al*., 1986). We have previously shown (Bronchti *et al*., 1989) that mole rats have a typical mammalian central auditory system: all major central auditory nuclei are easily identifiable and well-developed. Furthermore, 2-deoxyglucose (2DG; 2-fluoro-2-deoxy-D-[$^{14}$C(U)]-glucose) mapping of functional metabolic activity induced by auditory stimulation in unilaterally deafened mole rats revealed patterns of contralateral and ipsilateral auditory activity in these nuclei similar to those observed in other rodents.

In addition, these mapping experiments revealed strong auditory activation in a thalamic structure, located dorsolateral to the anterior part of the medial geniculate body (MGB) and which we believe to be the dLGB or a significant part thereof (Bronchti *et al*., 1989). Areas in the occipital cortex showed bilaterally asymmetric 2DG uptake in these animals, revealing strong auditory activation of occipital areas in addition to that of the temporal auditory cortex (Heil *et al*., 1991). Preliminary experiments disclosed single-unit responses to auditory stimuli in these occipital regions (Heil *et al*., 1991). Taken together, these data suggest an auditory take-over of the remnant thalamocortical visual pathway, or a significant part thereof, which is mediated by auditory projections from the inferior colliculus (IC) to the dLGB (Doron & Wollberg, 1994). The dLGB in turn has, as in other mammals, reciprocal connections with the occipital cortex, which would thus appear to represent the remnant visual cortex of sighted rodents (Cooper *et al*., 1993b; Doron & Wollberg, 1994).

Necker *et al*. (1992) mapped the cortex of *Spalax ehrenbergi* electrophysiologically for somatosensory, auditory and visual responses. They established that there was a well-developed somatosensory cortex with physiological characteristics and a somatotopic organization similar to those found in the rat and other mammals. The somatosensory area of the mole rat was larger than that of the rat (see also Mann *et al*., 1997) and extended further into the occipital cortex. They were unable to record visual or auditory responses caudal to the somatosensory area. Based on these data, Necker *et al*. (1992) concluded that in *Spalax* the area normally occupied by the visual cortex might serve a somatosensory function.

An important issue, still unresolved, is to examine to what extent the blind mole rat uses its occipital cortex. Which part of the normally visual cortex is activated by other modalities? Are the different sensory modalities reported as reaching this cortical area segregated into different functional fields or is the occipital cortex multisensory? In order to address these questions and to try to reconcile the apparently conflicting results of the different experimental approaches and their interpretations, a detailed survey of the occipital and adjoining cortices of *Spalax ehrenbergi* is necessary together with a reconstruction of auditory and somatosensory activated cortical regions with a common frame of reference.

## Materials and methods

All the procedures used in this study comply with the 'Principles of animal care', publication N°86–23, revised 1985, of the USA National Institutes of Health and were approved by the local animal care committees in Germany and Switzerland.

### *Animals*

Adult specimens of *Spalax ehrenbergi* (weighing 120–250 g) were trapped in the Tel Aviv region and in the northern part of the Negev desert in Israel. They were kept individually in separate cages under constant temperature conditions (22 ± 2 °C) and a light : dark regime of 10 : 14 h. Rodent chow was supplied *ad libitum* and sufficient fresh vegetables and fruits, which mole rats use as a source of water, were provided twice a week.

### *2-DG functional mapping*

#### *Auditory stimulation*

Auditory-activated cortical areas were examined in six unilaterally deafened (right ear intact) mole rats, one bilaterally deafened animal, and two intact controls. As the auditory system is largely decussated, unilateral deafening causes asymmetrical stimulation of the auditory projections and thereby an asymmetrical activation and labelling of the auditory system. This enables the identification of auditory-evoked 2DG uptake. Deafening was accomplished by a mechanical destruction of the middle and inner ear under deep halothane anaesthesia. In an approach through the external meatus, the tympanic membrane was slit and the inner ear crushed with a curette. The animals were treated locally with an analgesic. After recovery from anaesthesia, five of the six unilaterally deafened subjects and the bilaterally deafened animal showed signs of labyrinth impairment. These signs disappeared within two days and, in no case, were present during the 2DG experiment.

Two to three days after deafening, fully alert animals were injected intraperitoneally with 18–36 μCi/100 g body weight of 2-fluoro-2-deoxy-D-[$^{14}$C(U)]-glucose (2DG; Amersham, Germany) and immediately placed within a cage in a sound-attenuating chamber, where they were exposed to auditory stimuli. These stimuli consisted of 40-ms noise bursts shaped with 5-ms rise and fall times, emitted by a loudspeaker located 80 cm from the animal's cage. Bursts were presented in trains lasting 2 s with intertrain intervals of 0.5 s. The repetition rate of the bursts within each train was kept constant but varied randomly among trains between 1 and 20 bursts/s. Sound pressure levels were measured with a Brüel & Kjaer (Naerum, Denmark; model 2215) sound level meter and varied between ≈ 70 and 80dB sound pressure level (SPL; re 20 μPa) at different positions inside the cage and in different experiments. In order to reveal any possible contribution of light to the cortical 2DG labelling, three unilaterally deafened mole rats and one control animal were exposed to the noise bursts while the chamber was illuminated whereas the other animals were stimulated in the dark.

Ninety minutes after 2DG administration the animals were decapitated, their brains were quickly removed from the skulls and frozen on the stage of a cryostat. Serial 40-μm transverse or horizontal sections were cut and processed for film autoradiography. After development of the autoradiograms, the sections were stained with cresyl violet.

Densitometric analysis of autoradiographs were performed with a video-image processing system as previously described in detail (Bronchti *et al*., 1989). Autoradiographs were scanned by a video camera mounted on a zoom microscope, digitized, and converted into a matrix of 256 × 256 pixels with an 8-bit intensity resolution. The optical density (OD) of the corpus callosum obtained from one section per brain served as a constant reference value. All values of OD were expressed relative to the OD of the reference area and displayed as 32 horizontal profiles, spaced out at a constant distance. These displays resulted in pseudo-three-dimensional landscapes with

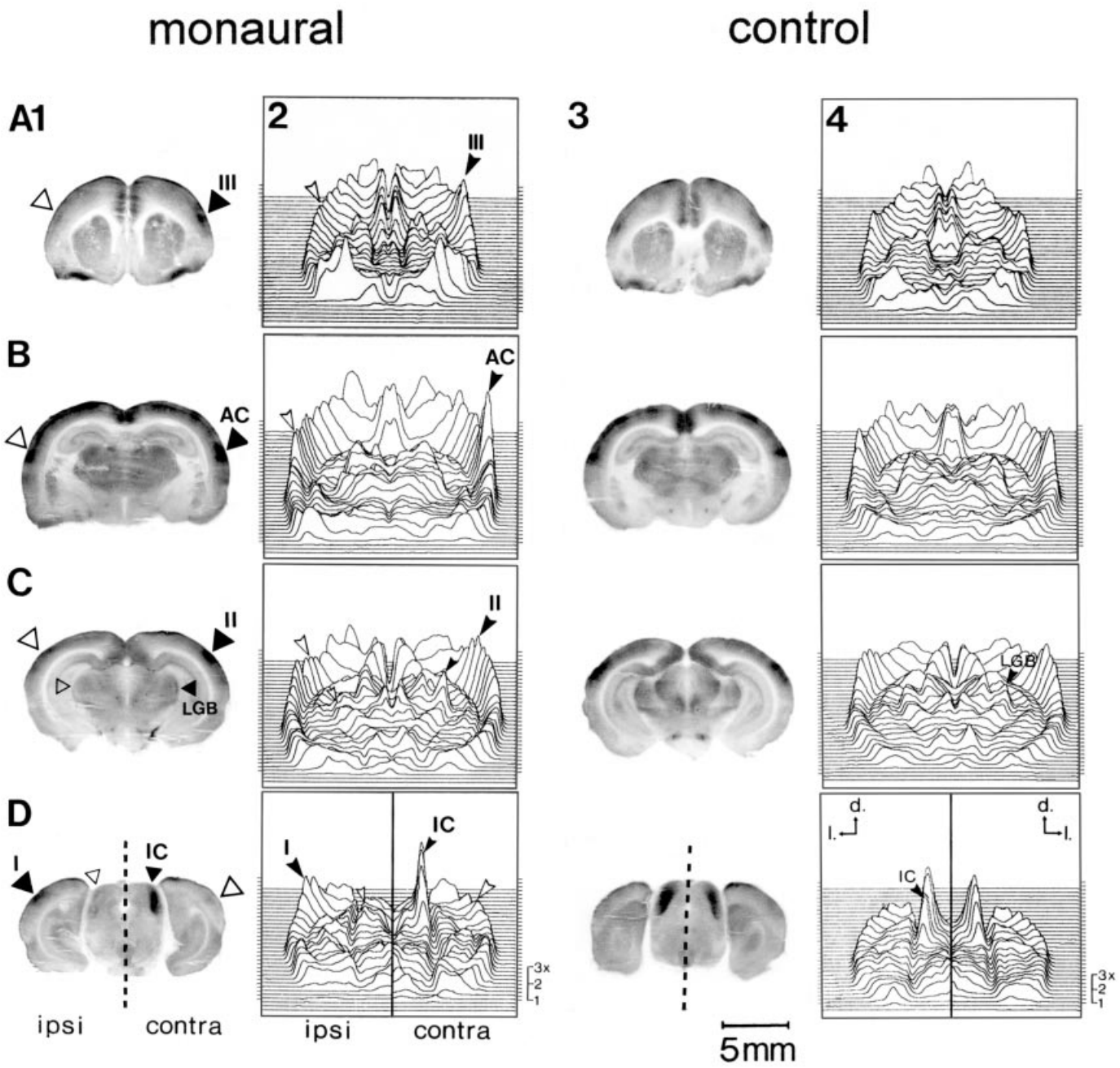



FIG. 2. 2DG autoradiographs of selected transverse sections from a noise-stimulated monaural mole rat (column 1) and an intact control (column 3) from (A) rostral to (D) caudal levels. Columns 2 and 4 show corresponding densitometric profiles. Intensity scaling given in D2 and D4 represents factors of background and apply to all densitometric charts in that column (see description in Materials and methods). Note the asymmetric 2DG uptake in the monaural case of cortical regions I, II, III, and auditory cortex (AC), as well as in the inferior colliculus (IC) and the dorsal lateral geniculate body (LGB). In the control animal all these structures are symmetrically labelled. Other conventions as in Fig. 1. When a brain was cut slightly skewed, care was taken to calculate the degree of symmetry (or of asymmetry) between the hemispheres at corresponding rostrocaudal levels (note, for example, that in row D corresponding hemisections were in different sections).

peaks of relative optical density (rOD) representing high 2DG uptake (see Fig. 2).

From the densitometric profiles, rOD values of the relevant cortical locations (large arrowheads in columns 1 and 2 of Fig. 2) were extracted and the degree of asymmetry or symmetry of 2DG labelling in the two hemispheres was expressed by an index *S*, defined as:

$$S = (c - i)/(c + i)$$

where *c* and *i* represent the rOD values at corresponding cortical loci in the contralateral (*c*) and ipsilateral (*i*) hemisphere. For intact controls, *c* and *i* were substituted by rOD values obtained from the right and left hemispheres, respectively. Thus, a symmetry index *S* of zero represents symmetric 2DG labelling at the corresponding loci in the two hemispheres, while positive and negative values of *S* indicate stronger 2DG labelling in the contralateral (or, in controls, in the right) and in the ipsilateral (left) hemisphere, respectively. We used additional references, such as the form of the hippocampus, to ensure that comparisons of 2DG labelling in the two hemispheres were made at corresponding locations.

*Vibrissal stimulation*

To examine the possibility of overlap between auditory and somatosensory responsive areas in the mole rat's occipital cortex we also employed the 2DG technique with vibrissal stimulation. The cortical representation of the vibrissae, as determined electrophysiologically, is within caudal parts of the somatosensory cortex, close to or in an area occupied by visual cortex in sighted rodents (Necker *et al*., 1992). The mole rat has short mystacial vibrissae organized in a regular mammalian pattern (Klauer *et al*., 1997) although it does not whisk. Two hours before the experiment, one mole rat was lightly anaesthetized with Rompun 0.2%, 0.3 mL/kg body weight (Bayer, Germany) and Ketalar, 27 mg/kg body weight (Parke Davis, USA) and pieces of metal wire, 1.5 mm long and 0.2 mm in diameter, were glued onto six whiskers: four arranged roughly in one rostrocaudal row and three aligned along one dorsoventral arc on the left whiskerpad (one stimulated whisker appertained to both the row and the arc). All other whiskers on the left and right sides were clipped. The animal was then restrained on a polystyrene foam cast with adhesive tape. After recovery from anaesthesia, the animal was placed in the Lausanne whisker stimulator (Melzer *et al*., 1985), injected with [1–$^{14}$C]2-deoxy-D-glucose in saline (New England Nuclear, DuPont de Nemours and Co., Germany; 20 μCi/100 g body weight), and immediately exposed to magnetic field bursts (7.4 bursts/s) for 90min. At the end of the experiment we observed that one of the metal pieces, the one placed on the most ventral whisker on the arc, was absent. The animal was then killed with a lethal dose of pentobarbitone, perfused through the heart with a 3% solution of formalin in neutral phosphate buffer, and the brain was extracted from the skull and frozen on dry ice. Coronal 20-μm sections were cut on a cryostat, mounted on gelatin-coated slides, dried at 60 °C on a hotplate, and processed for film autoradiography (Cronex MRF31, Dupont de Nemours, Germany). After development of the autoradiograms, the sections were stained with cresyl violet.

### *Electrophysiology*

Electrophysiological recordings were made from the occipital cortices of 27 deeply anaesthetized mole rats. This subterranean rodent has, normally, very low metabolic, respiratory and heart rates (Arieli *et al*., 1977; Storier *et al*., 1981). The heart rate is also highly arrhythmic, a condition that is further exacerbated by anaesthesia. Deep and prolonged surgical anaesthesia is therefore difficult to obtain. We achieved a moderately stable and nonfatal anaesthesia with intramuscular injections of a combination of Rompun 0.2% (Bayer, Germany, 0.3 mL/kg body weight) and Ketalar (Parke Davis, USA, 27 mg/kg body weight). Throughout the experiment the anaesthesia was maintained by supplementary doses of Ketalar (10 mg/kg body weight) administered subcutaneously. Anaesthetized animals were restrained in a specially designed stereotaxic apparatus that made the use of ear-bars unnecessary. The posterior skull was exposed by gently separating the relatively large head muscles, and a circular craniotomy was performed unilaterally over the left occipital cortex. The dura was left intact and the brain was covered with paraffin oil. All recordings were conducted within a double-walled sound attenuating chamber (IAC 1203A; Industrial Acoustics Co., New York, USA).

Our standard auditory stimulus repertoire consisted of 0.2-ms clicks, white noise (0.02–20 kHz) produced by a noise generator (Brüel and Kjaer 1405; Naerum, Denmark), and pure tones generated by a voltage-controlled oscillator (Wavetek 136, San Diego, USA). Noise and tones were shaped into 200-ms bursts with 20-ms rise and fall time. Pure tones covered a frequency range of 0.1–1.3 kHz in 16 linear steps of 80 Hz, and a range of 1.0–14.0 kHz in 64 linear steps of 203 Hz. Clicks and noise bursts were presented at a rate of one per 3 s with 15 consecutive repetitions of each stimulus. Amplitudes were controlled by means of a custom-made power amplifier and a manually operated attenuator (HP 350D Hewlett-Packard). Stimuli were delivered through precalibrated earphones (Azden, Azden corporation; New York, USA) which were either connected to the ears through short plastic specules or, in later experiments, were positioned close to the opening of the external auditory canal without touching the skin. The signals were presented binaurally or monaurally, either contralateral or ipsilateral to the recording side. Calibration of the sound delivery system was accomplished by placing a calibrated condenser microphone (Brüel & Kjaer 4134) in the same location as the animal's ear, simulating the experimental conditions. Sound pressure levels (in dB re 20 μPa) were measured with a sound level meter (Brüel & Kjaer 2209) which was serially connected to a 1/3 octave filter set (Brüel & Kjaer 1616). The frequency response of the earphones was flat (± 5dB) throughout the frequency range of 70Hz–16 kHz.

Single-unit activity was recorded extracellularly by means of glass-coated platinum–iridium microelectrodes which were advanced through the dura, normal to the brain surface, by a remotely controlled stepping motor. Cellular activity was amplified, filtered (Digitimer Neurolog System; Digitimer Research Instrumentation, England), monitored for shape and size, discriminated from background activity by a window discriminator (World Precision Instruments #121, USA) and digitized. Discriminated spikes were displayed on-line as dot-raster and stored for off-line analyses. Evoked field potentials were picked up by the same microelectrodes, AC-amplified, filtered (bandwidth 0.05–5.0 kHz), averaged (RC Electronics, Oregon, USA), displayed on line and stored for off-line analyses. The mediolateral and anteroposterior coordinates of the micromanipulator were determined, with 100-μm accuracy, for each recording site and the position of each site referred to its distance from the midline and from the anterior border of the straight part of the lateral sinus, which was readily visible through the bone. While the 100-μm accuracy of the manipulator might be not adequate for the fine-grain mapping of a small rodent visual cortex (this distance corresponds to 4–5° of arc in the mouse occipital cortex (see fig. 1 of Gordon & Stryker, 1996), it was sufficient for our purpose, particularly when considering the precision of the other mapping methods we used (see below). Small lesions along selected electrode penetrations allowed later reconstruction of recording sites also with respect to an internal anteroposterior reference, viz., the splenium of the corpus callosum (see below), which was easily recognizable in Nissl-stained sections prepared from these brains.

### *Histology*

All sections subjected to 2DG autoradiography were also stained for Nissl substance with cresyl violet. Sections from two additional brains were stained for Nissl substance and for myelin. These latter two animals were perfused through the heart, under deep anaesthesia, with physiological saline containing heparin (1000 units/L) followed by 10% neutral formalin. One brain was embedded in paraffin and 15-μm serial frontal sections were stained applying the Klüver and Barrera (1953) method. The other brain was frozen and 40-μm serial frontal sections were stained for myelin with a modification of the Heidenhain procedure (Hutchins & Weber, 1983). Relevant sections were either photographed or digitized through a video camera mounted on a microscope. The latter were processed with Corel Photo-Paint™ software (Corel Corporation, USA) for presentation.

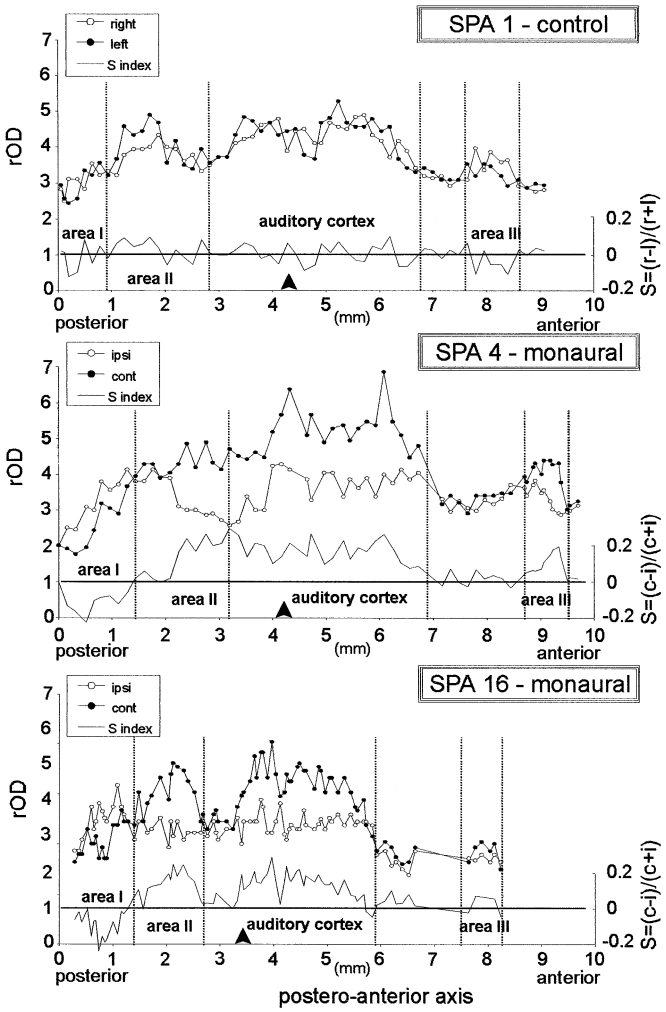



FIG. 3. Relative optical density (rOD; left ordinates) of 2DG uptake in cortical areas of interest and plotted against the posteroanterior axis. Data from a noise-stimulated control (SPA 1) and from two monaural cases (SPA 4 and SPA 16) are shown. For each animal, the rODs of corresponding areas in the contralateral and ipsilateral hemispheres, as well as the symmetry index S (right ordinates), which was calculated from the rOD values (see text), are plotted. Arrowheads on the abscissae indicate the level of the splenium of the corpus callosum. Note the relatively symmetrical 2DG labelling in the cortex of the control animal and the asymmetrical 2DG labelling in the monaural cases.

### *Spatial reference system*

It was particularly important to compare the cortical locations of the auditory- and somatosensory-induced 2DG label, of the electrophysiological recording sites and of the cyto- and myeloarchitectural features found by us with those of the somatosensory and auditory representations published by Necker *et al*. (1992), and with those of tracer injection sites illustrated by Rehkämper *et al*. (1994). For this purpose we adopted their schematic dorsal view of the brain of *Spalax* and their coordinate system (see figs 2–4 in Necker *et al*., 1992 and fig. 4 of Rehkämper *et al*., 1994), and the midline and the splenium of the corpus callosum served as common reliable internal references for orientation along the mediolateral and anterior–posterior axes, respectively. In addition, we used the dorsal border of the corpus striatum as a dorsoventral reference as its usefulness had been established previously in similar experiments in gerbils (e.g. Scheich *et al*., 1993). All internal references are readily identifiable in Nissl- and myelin-stained material, as well as in 2DG autoradiographs. Each brain from the 2DG experiments which had been cut coronally was subjected to a computerized 3-D reconstruction. To that end all autoradiographs were digitized with a CCD camera (768 × 512 pixel, 8 bit/pixel). Each slice was preprocessed by a *z*-transformation (subtraction of the mean divided by the SD) in order to reduce individual grey values. Then each single image of one brain was aligned with its neighbours by translating and rotating each slice in order to reconstruct the original 3-D object. We used a combined method of principal axes alignment followed by a cross-correlation method. This approach is fully automatic and a very fast technique for obtaining the required transformations (Hess *et al*., 1998). Afterwards, all the obtained 3-D volumes were registered to each other using a 3-D principal axes alignment approach. The 3-D datasets were smoothed (averaging each 3 × 3 × 3 pixel cube) and histogram-equalized in order to enhance the labelling contrast. Next, warping was performed: warping, as nonlinear geometric transformations (Wolberg, 1990; Toga, 1994), can be used to reduce geometric variations by transforming an individual dataset to a reference system, e.g. a 'standard brain'. Therefore, warping can be used for an accurate comparison of interindividual 3-D brain datasets. In order to perform a warp, spatial correspondence between the datasets has to be determined. In our case the correspondence is landmark-based by a 3-D differential operator (Rohr, 1997; Pielot *et al*., 2001). Then, the datasets are transformed using a specifically developed distance-based warping function. To ensure the best possible warping quality, the warping process itself is optimized by an evolutionary optimization strategy (see Pielot *et al*., 2001). After warping increased the similarity between the datasets, the individual brains were averaged (pixel-based) to obtain the 'average brain'.

The datasets were visualized in the program AMIRA (Indeed GmbH, Germany). Besides sophisticated visualization capabilities (pixel- and surface-based), this program is also capable of calculating a connected-component analysis (CCA). Due to the preprocessing (especially the *z*-transformation and the histogram equalization), it was possible in all the datasets to obtain the labelled volumes using the CCA with the following object model: grey-value range 0 (black) to 20 and a minimum volume of 200 voxels. The outer contour of the obtained objects (connected voxels) in the areas of interest were manually colour-coded. From this intermediate information a triangulation of the corresponding surfaces for each object was obtained. These surfaces were rendered according to the chosen colour scheme. The same procedure was performed with the grand average brain.

The presentation of results obtained from different experiments performed on different animals onto one 'typical' brain is obviously of limited precision. Interindividual variation is significant in wild animals (as can be seen, for instance, in the size of the brains presented in Fig. 3). We corrected for such variability by rescaling each individual map to fit the standard brain.

## Results

### *2DG mapping of auditory-responsive areas*

In unilaterally deafened mole rats exposed to white noise bursts, large areas of neocortex dorsal to the rhinal fissure were asymmetrically labelled with 2DG, as shown in a montage of transverse sections in Fig. 1 (bottom). Under the same experimental conditions, these regions were symmetrically labelled in intact mole rats (Fig. 1, top), indicating that the asymmetrical labelling in unilaterally deafened

animals was indeed due to auditory activation. Based on the comparison of these labelling patterns with similar experiments in the Mongolian gerbil (Caird *et al*., 1991), these areas were tentatively assigned to different fields of the auditory cortex. A primary field (AI) is located in temporal cortex at an anteroposterior position around the splenium of the corpus callosum and at a dorsoventral position extending ventrally from the dorsal border of the striatum. AI was labelled more strongly in the hemisphere contralateral to the intact cochlea (see +AI+ in Fig. 1, bottom). Directly anterior and mostly ventral to AI lies an anterior auditory field (AAF), also labelled more strongly in the contralateral hemisphere (just dorsal to the label AAF in Fig. 1, bottom). Ventral and posterior to AI, and just above the rhinal fissure, there may be further auditory regions (ventral and posterior auditory fields, labelled V and P in Fig. 1, bottom). 2DG labelling in these regions was weak relative to that in AI and AAF and, hence, hemispheric asymmetries were not very obvious. However, based on their positions relative to one another and to the topographical landmarks, it seems that these temporal cortical regions correspond to regions or fields of the auditory cortex of other rodent species, determined by various experimental procedures such as electrophysiology, cytoarchitecture and 2DG labelling (e.g. Hellweg *et al*., 1977; Ryan *et al*., 1982; Paxinos & Watson, 1986; Caird *et al*., 1991; Scheich *et al*., 1993; Thomas *et al*., 1993; Budinger *et al*., 2000a; Budinger *et al*., 2000b).

Unlike in other rodents, however, pronounced asymmetries of 2DG uptake in unilaterally deafened mole rats were also observed in two regions of the occipital cortex that topographically correspond to rodent visual cortex (e.g. Caviness., 1975; Paxinos & Watson, 1986; Zilles, 1986:). A most dorsocaudal region, extending for ≈ 2.0 mm along the mediolateral and for ≈ 1.0 mm along the anteriorposterior axis, arbitrarily termed 'area I' (just dorsal to the line labelled I in Fig. 1), showed stronger 2DG uptake in the ipsilateral hemisphere. A second region, termed 'area II', was located anterior and slightly ventral to area I, but still ≈ 4 mm dorsal to the rhinal fissure and also dorsal to what we assume are the posterior fields of the mole rat's auditory cortex (label +II+ dorsal to the black line in Fig. 1, bottom). Area II extended for ≈ 1.6 mm along the mediolateral and for ≈ 1.5 mm along the anteroposterior axis, and showed stronger 2DG uptake on the contralateral side.

Another, relatively small, region (area III), located in the parietal cortex, ≈ 4 mm anterior to the centre of auditory cortex, also showed an asymmetric 2DG uptake, with stronger labelling in the contralateral hemisphere, in unilaterally deafened mole rats (label +III+ dorsal to the black line at right in Fig. 1).

We did not observe any difference between animals acoustically stimulated in the dark vs. those stimulated in the illuminated chamber.

The degree of 2DG labelling, and of interhemispheric asymmetries, in the temporal, occipital and parietal cortices of intact and unilaterally deafened mole rats was quantified by densitometric analyses. This is illustrated in Fig. 2 where two series of autoradiographs of transverse sections at selected levels are presented along with the corresponding densitometric profiles. The asymmetrical label of the dorsal lateral geniculate body (labelled LGB in the figure) and the inferior colliculus (IC) is also obvious (for details regarding auditory activation of subcortical areas see Bronchti *et al*., 1989).

Figure 3 represents rOD values, along the posteroanterior axis, from the left and right cortices of an intact mole rat (control; top) and from the contralateral and ipsilateral cortices of two unilaterally deafened mole rats (middle and bottom), as well as the derived symmetry indices (S). In the control animal, S-values along the entire posteroanterior axis fluctuate randomly above and below zero, indicating an overall symmetrical 2DG labelling in the two hemispheres. In unilaterally deafened mole rats, however, S-values deviate systematically from zero. In the occipital area 'I' all S-values are in essence negative, reflecting stronger labelling in the ipsilateral cortex. Anterior to area I, within the occipital area II, within the auditory cortex and within the parietal area III, nearly all S-indices are positive, reflecting more prominent labelling in the contralateral cortex. In the unilaterally deafened animals (SPA 4 and 16 in Fig. 3), the boundary between areas I and II was characterized by a reversal of the sign of S at ≈ 1.4 mm (in these cases) from the occipital pole.

Figure 4 shows a fine-grain analysis of 2DG labelling with respect to the cortical layers. In all areas the most intensive 2DG label was found in layer IV, the main target of thalamic afferents. Whereas 2DG label was considerably weaker in the infra- and supragranular layers in contralateral areas I and III, strong 2DG label extended from the granular layer up to the supragranular layers in ipsilateral area I, and in contralateral area II and AC (auditory cortex).

### *Cortical activation by vibrissal stimulation*

Figure 5 shows a montage of 2DG autoradiographs of transverse sections through the brain of the mole rat that had been subjected to vibrissal stimulation. The unilateral stimulation of one row and one arc of mystacial whiskers caused a sharp band of 2DG label, running along the anteroposterior axis of only the contralateral parietal cortex (just dorsal to the dorsal white line in Fig. 5). The band was ≈ 2.5–3 mm long and posteriorly extended ≈ 1 mm beyond the splenium of the corpus callosum and corresponds to activation of the whisker representation within primary somatosensory cortex. The band's thickness increased by a factor of ≈ 2 in several consecutive sections near its anterior end. Lateral to this prominent band, and just around the caudal end of the splenium of the corpus callosum, was another contralaterally labelled cortical area (dorsal to the ventral white line in Fig. 5), albeit smaller and less sharply delineated. It probably corresponds to activation of whisker representation within the secondary somatosensory cortex. No such label was present ipsilaterally.

To compare the cortical maps obtained with unilateral ear or vibrissal stimulation on the one hand, and other experimental procedures on the other hand, precise 3-D reconstruction of the labelling pattern was performed (see Materials and methods section). The procedure and results of this reconstruction are presented in Fig. 6 for two unilaterally deafened animals with emphasis on the location of auditory and somatosensory responsive areas. Later on, in Fig. 7A and B, the cortical patterns observed in all four coronally cut unilaterally deafened cases are presented after averaging, for their comparison with electrophysiological and histological data, respectively.

The temporal auditory cortices are located mainly on the lateral aspects of the cerebral hemispheres and their extent in *Spalax* is best appreciated in the dorsolateral and anterior views provided in Figs 6A and B. However, the topographic relationship between the auditory-responsive fields in the occipital cortex and the somatosensory maps are most clearly seen in dorsal views presented in Fig. 6C–F. They reveal that both auditory-responsive occipital areas are located posterior to the caudal boundary of the somatosensory representation, as mapped by Necker *et al*. (1992), and more medial than the pocket of auditory responses found by these authors (labelled 'A' in panels E and F). The overlap between areas I and II on the one hand, and the somatosensory cortex on the other, seems minimal. Area III appears to correspond to the region around the representation of the lower or the upper jaw within the somatosensory cortex.

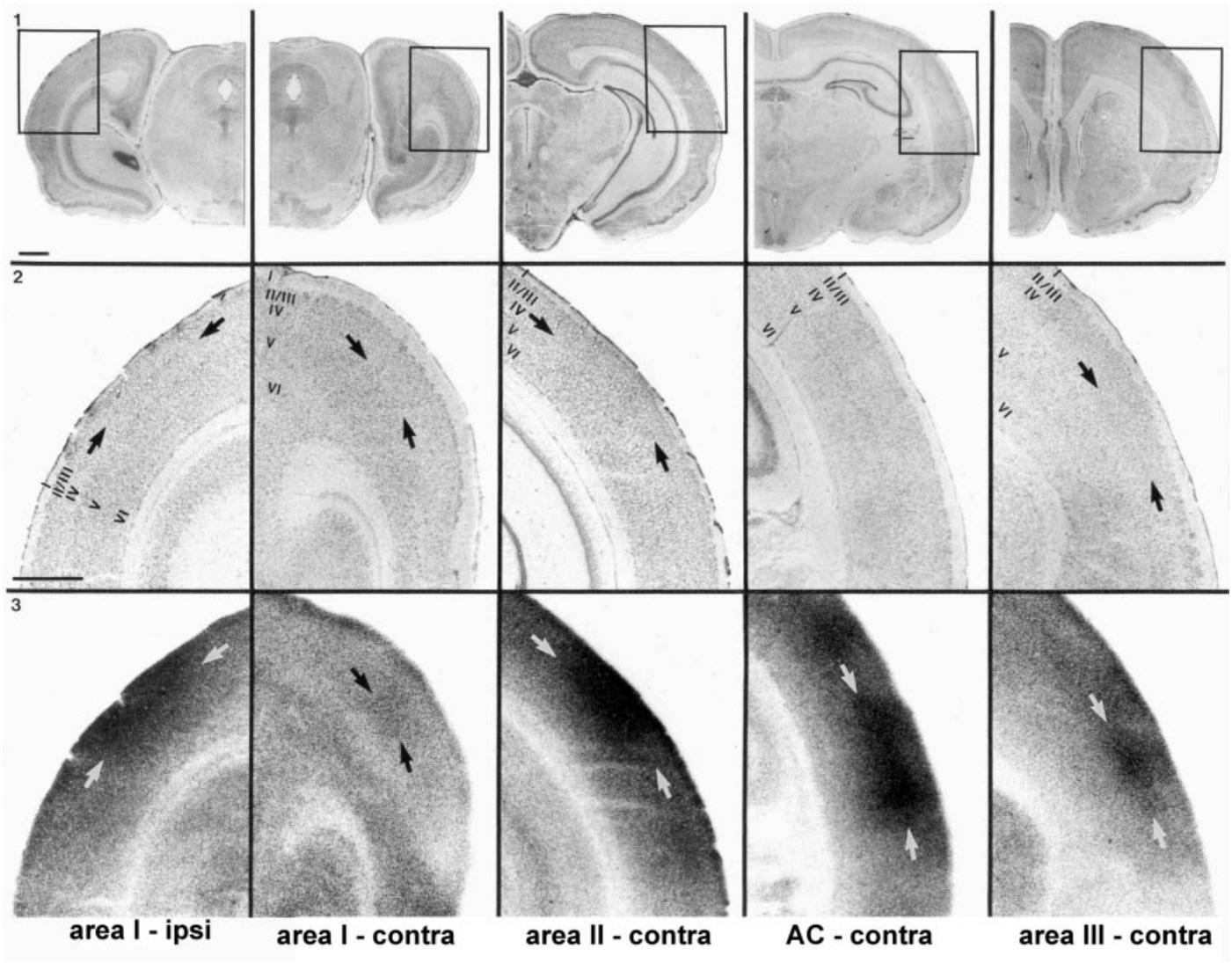



FIG. 4. Layer-specific distribution of 2DG label in the auditory-activated occipital, temporal and parietal cortex in a monaural mole rat. The different cortical areas are specified at the bottom of each column (I ipsi, I contra, II contra, AC contra and III contra). (Upper row) Frontal hemisections stained for Nissl substance. (Middle row) Enlargements of the areas framed in row 1. (Lower row) Corresponding 2DG autoradiographs. Arrows point towards layer IV. Note that the uptake of 2DG in the auditory cortex (AC) and region III is maximal in layer IV whereas in regions I (ipsilateral) and II, 2DG uptake is similar in the granular and the supragranular layers. Scale bars, 1 mm.

Figure 6E and F also shows that both cortical regions activated by the vibrissal stimulation in our 2DG experiment fall entirely within the area of vibrissal representation as established electrophysiologically by Necker *et al.* (1992) (V in Fig. 6E). The representation of the stimulated whiskers extends relatively far caudal close to the caudal boundary of the vibrissal representation delineated by Necker *et al.* (1992).

### *Electrophysiology*

In unilaterally deafened animals the 2DG procedure can unequivocally localize targets of auditory input when these targets are labelled asymmetrically, as compared with intact animals where the label is symmetrical. However, there may be neural substrates that show symmetrical 2DG uptake in unilaterally deafened animals, and yet receive auditory input, e.g. nuclei that receive similar excitatory inputs from the two ears (e.g. Heil & Scheich, 1986). Comparing 2DG labelling in normal and bilaterally deafened animals may unveil some of those targets. This approach works well for structures that have dominant auditory input such as brainstem nuclei (e.g. Heil & Scheich, 1986; Bronchti *et al.*, 1989). However, for nonprimary auditory areas, where auditory input is relatively weak, a decrease of 2DG uptake, if any, following bilateral deafening, may not be seen. To reveal such potentially auditory-activated areas in the blind mole rat's occipital cortex (beyond areas I and II identified with 2DG) and to corroborate our 2DG findings, we therefore also used electrophysiological recordings.

Field potentials evoked by auditory stimuli (clicks, noise, and tone bursts) were recorded from the surface or within the cortex of three anaesthetized mole rats. Figure 7A shows the reconstructed locations of electrode penetrations over the left occipital cortices of these animals in relation to the 2DG ipsilaterally labelled areas averaged from four unilaterally deafened mole rats. Filled symbols identify

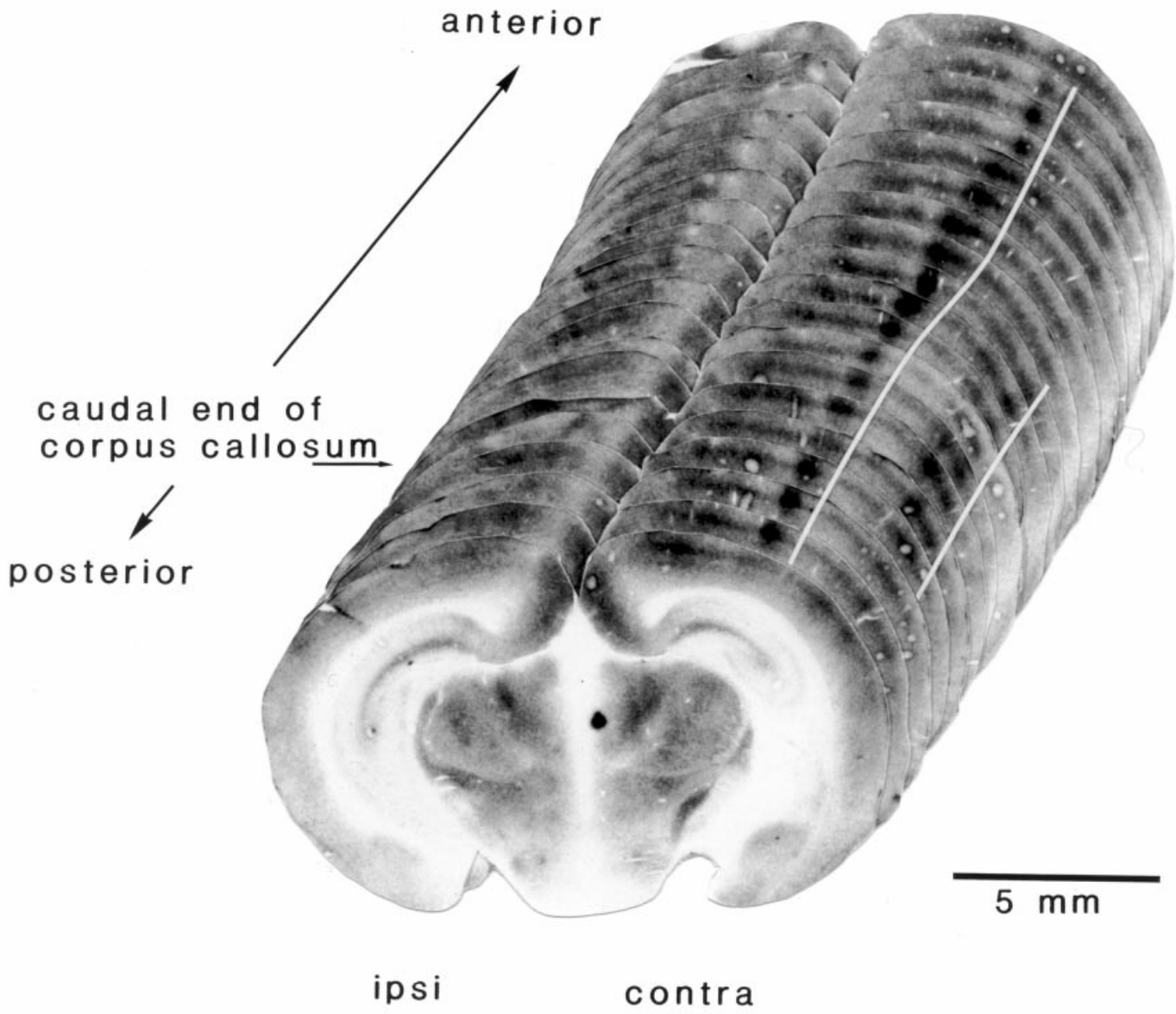
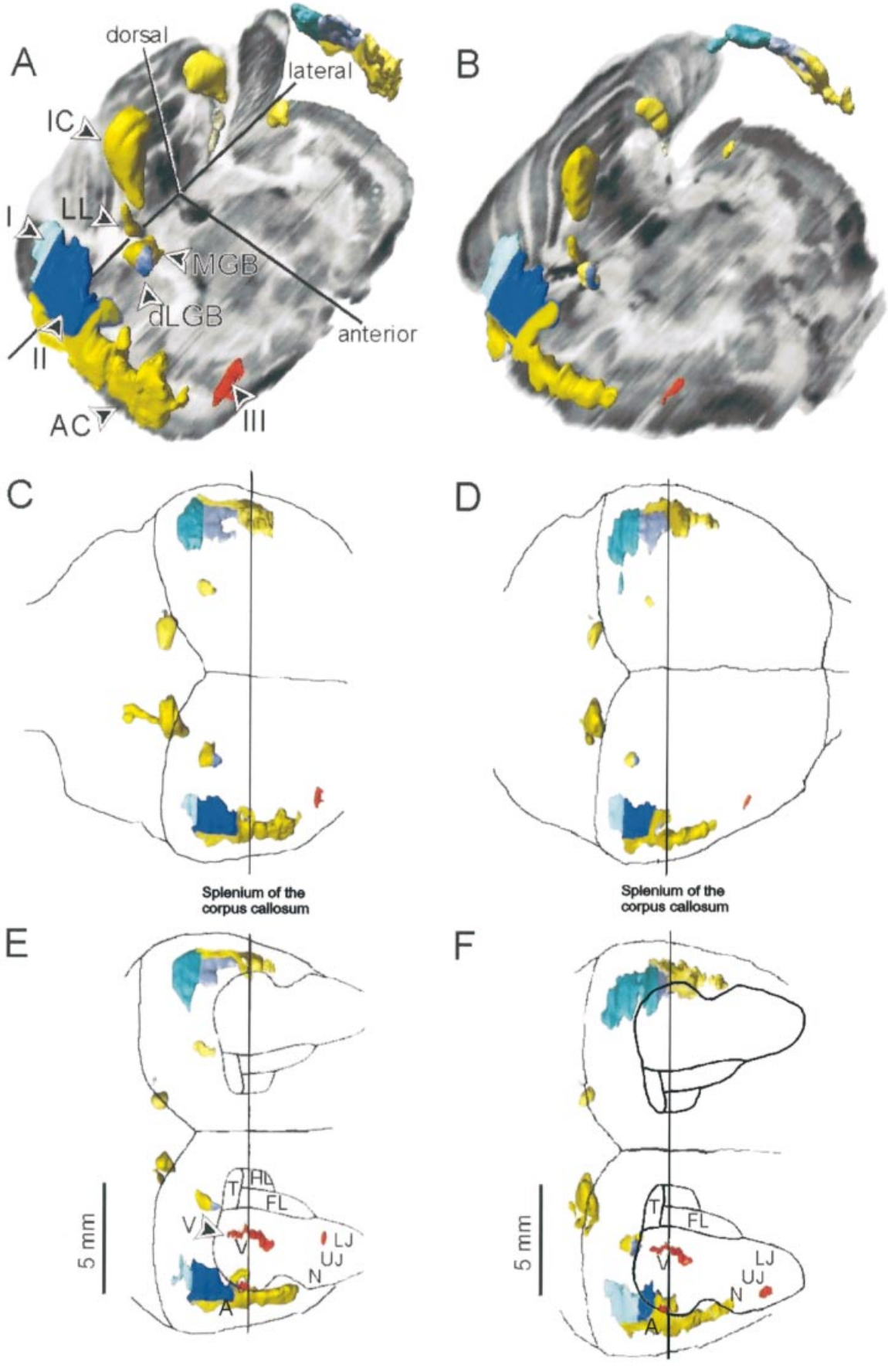



FIG. 5. Overview of cortical 2DG labelling in a mole rat in which one row and one arc of vibrissae on the left whiskerpad were stimulated. Photographs of autoradiographs from coronal sections were mounted from rostral (top right) to caudal (bottom left) along an oblique line so that all but the relevant regions of cortex of each hemisection are covered by the adjacent more posterior one. Average interval between sections is 160 μm. A sharp band of 2DG label dorsal to the dorsal white line and more fuzzy label dorsal to the ventral white line are present only in the hemisphere contralateral to the stimulated vibrissae and are located within the somatosensory cortex (see Figs 6E and F).

sites responsive to, and open circles sites unresponsive to, auditory stimulation. The filled stars point to the location of those recording sites, all responsive to auditory stimuli, that are shown in Fig. 8, as based on lesions along the second most lateral track (labelled 'i' in Figs 7A and 8). Note that some auditory-responsive sites overlap with areas I and II but that responsive sites were also found medial to area I.

Examples of field potentials evoked by clicks are shown in Fig. 9. Panel (a) depicts a response recorded laterally to area II, in an area that presumably corresponds to posterior auditory cortex. This biphasic response consists of a large, relatively short negative deflection with ≈30 ms peak latency, followed by a more prolonged positive component. In contrast, evoked field potentials in the occipital cortex started, in most cases, with a positive-going component of ≈40–60 ms peak latency. Contralateral stimulation was always more effective, evoking more prominent, often multiphasic, responses than ipsilateral stimulation which generally yielded monophasic responses. In correspondence with the 2DG results, ipsilateral responses could be elicited in area I (penetrations b, c and d), whereas only very small ipsilateral responses could be evoked medial to area I or in area II (penetrations f, g and h).

Extracellular activity was recorded from a total of 325 single units, isolated along 55 electrode penetrations distributed over the occipital cortex of 24 blind mole rats. About 60% of these units, many of which were located within the 2DG-labelled occipital regions I and II, responded to at least one type of auditory stimulus of our standard repertoire (clicks, noise and tone bursts). However, it appeared that auditory units were also found medial to these areas, where no 2DG


A
dorsal
lateral
IC
I
LL
MGB
dLGB
anterior
II
AC
III
B
C
Splenium of the corpus callosum
D
Splenium of the corpus callosum
E
5 mm
T
RL
FL
V
V
LJ
UJ
N
A
F
5 mm
T
FL
V
LJ
UJ
N
A

hotspot was encountered in either intact or unilaterally deafened mole rats. Auditory-responsive units in these regions were less readily isolated than were those more lateral. A few representative recording sites are presented on the right hemisphere in Fig. 7B while the corresponding single cell responses are illustrated in Fig. 10.

Thresholds tended to increase with time in the course of an experiment, probably due to the high susceptibility of the animal to anaesthesia. Latencies of units to clicks of 80 dB (SPL peak intensity) ranged between 18 and 139 ms, with a mean (± SD) of 39 ± 21 ms. Latencies of ≈85% of the cells ranged between 20 and 40 ms. All minimum thresholds of single units to tone bursts were >60 dB SPL as determined audio-visually. The best frequencies ranged between ≈0.1 kHz and ≈5 kHz, matching well the behavioural hearing capability of this animal to airborne sounds (Bronchti *et al*., 1989; Heffner & Heffner, 1992). Response patterns (Fig. 10) were quite diverse with most of them comprising an onset excitatory component (our unpublished observations').

### *Anatomical definition of the primary visual cortex*

In the absence of visual activity, the definition of a cortical area as a remnant of a 'phylogenetic' visual cortex can be based only on anatomical data (cyto- and myeloarchitecture) and on connectivity patterns. A cortical profile characteristic of a primary visual area, as can be seen in the mouse (Caviness. (1975) or in the rat (Zilles, 1986), is present (Fig. 11): its layer IV is wider than that of other parts of the occipital cortex, and the sublaminae Va and Vc are fairly distinct as hypocellular layers. Myelin stain of corresponding sections from another animal reveals a significant entry of myelinated fibres into this area, contrasting with the weaker staining of the surrounding fields (Fig. 12). A reconstruction of the primary visual cortex according to these two criteria (Fig. 7B) shows that the mole rat's putative area 17 encompasses only the most medial part of area I as determined by the 2DG experiments and extends more medially (note that the cortical profile illustrated in Fig. 11 corresponds to area I).

## Discussion

In this study we have shown that large areas of the cortex of the blind mole rat can be activated by auditory stimulation. Some areas are located in the temporal cortex, apparently constituting typical auditory fields. However, in addition, areas within the occipital and parietal cortices were also activated by auditory stimuli.

### *Temporal cortex*

The location of auditory-activated areas within the temporal cortex was similar to the location of auditory cortex in other small rodents (for a review see Thomas *et al*., 1993), including the Mongolian gerbil. In the latter species, several distinct fields of auditory cortex have been identified with electrophysiological recording of neuronal responses to auditory stimuli (Thomas *et al*., 1993) as well as with 2DG mapping of functional metabolic activity (Caird *et al*., 1991; Scheich *et al*., 1993). Based on a comparison with the 2DG patterns observed in the gerbil in these latter studies, we also subdivided the temporal auditory cortex of the mole rat and suggested the existence of a primary auditory field AI and an anterior auditory field AAF, as well as ventral (V) and posterior (P) auditory regions. However, an electrophysiological survey of the temporal cortex will be necessary to unequivocally distinguish auditory fields.

### *Auditory-activated occipital and parietal areas*

Our 2DG data revealed two auditory-activated regions (named areas I and II) in the occipital cortex. Area I was labelled more strongly ipsilateral, and area II more strongly contralateral, to the intact ear. The presence of a relatively strong 2DG label in supragranular layers suggests that some of the auditory activation of areas I and II may be mediated by intracortical connections between auditory areas in the temporal and the occipital cortices. Such connections have been described in other rodents (Miller & Vogt, 1984; Budinger *et al*., 2000a). The auditory activation of these occipital areas was confirmed electrophysiologically, both with auditory evoked potentials and with single-unit recordings. The auditory evoked potential recorded very laterally (site 'a' in Fig. 7), i.e. in presumed posterior regions of the temporal auditory cortex, was similar in shape to those recorded by Necker *et al*. (1992) at a similar location. Potentials recorded more medially in occipital cortical regions were of more complex shape, again possibly reflecting a mixed input of cortical and thalamic origin. In the occipital regions corresponding to area I of unilaterally deafened mole rats we did observe relatively strong and reliable ipsilateral auditory evoked activity (Figs 9 and 10).

Cells in the occipital cortex of the mole rat responded to auditory stimuli such as clicks, tones and noise bursts. Most common were transient onset responses of relatively short latencies (most between 20 and 40 ms). Thresholds to tones were relatively high (> 60dB SPL), a fact that in part may be attributable to the use of long (viz. 20-ms) rise times (see Heil, 1997a; Heil, 1997b). Units were tuned to frequency, and best frequencies covered most of the species' audible

FIG. 6. Computer-aided 3-D reconstruction of the cortical (and some subcortical) labelling pattern observed in two monaural mole rats, SPA4 (left column) and SPA16 (right column). (A and B) Oblique view (from dorsal, lateral and anterior) of the asymmetric 2DG labelling pattern as reconstructed from serial transverse sections. The hemisphere which appears to be right is the left, contralateral to the intact ear. One reconstructed horizontal section and one coronal section passing through the inferior colliculus are presented in grey levels as a frame on which structures of interest are added in colour. Those were reconstructed by setting 2DG labelling intensity thresholds. Different thresholds were used for different structures but the same threshold was conserved for a given structure on the two sides of the brain. Structures in yellow are classical auditory ones: viz. lateral lemniscus (LL), inferior colliculus (IC), medial geniculate (MGB) and auditory cortex (AC). The darkish blue represents area II, the bright blue area I, the grey–blue the dorsal lateral geniculate body (dLGB) and the red area III. Comparing the two sides of the brain, paler colours represent weaker labelling. Black lines were added for the orientation. (C and D) Dorsal view of the reconstructed 2DG labels shown in A and B, respectively. The brains' contours were drawn as solid black lines. Note the differences between the two animals in the size and appearance of these contours. (E and F) The same dorsal view of the brains presented in C and D after the warping procedure was applied (see Materials and methods section). As a result of the warping, the two brains are more similar in shape and the labelling patterns can be easily compared. On these contours was added, in red, the 2DG label obtained with the vibrissal stimulation (see Fig. 5). This latter was reconstructed following the same computerized procedure. Finally, the somatosensory map drawn by Necker *et al*. (1992) was superimposed on these dorsal views using the midline and the posterior end of the corpus callosum as references. Because of the thresholding procedure, the cortical label is restricted to layer IV and therefore appears slightly medial to the lateral contour of the hemispheres. Note that the sites of 2DG uptake evoked by vibrissal stimulation are consistent with the electrophysiologically recorded somatosensory representation of Necker *et al*. and that the auditory-activated occipital areas I and II are obviously caudal to the somatosensory cortex. Also note that the location of parietal region III is close to the somatosensory representation of the jaws. Abbreviations: FL, front limb; HL, hind limb; LJ, lower jaw; N, neck; T: torso; UJ, upper jaw; V, vibrissae.

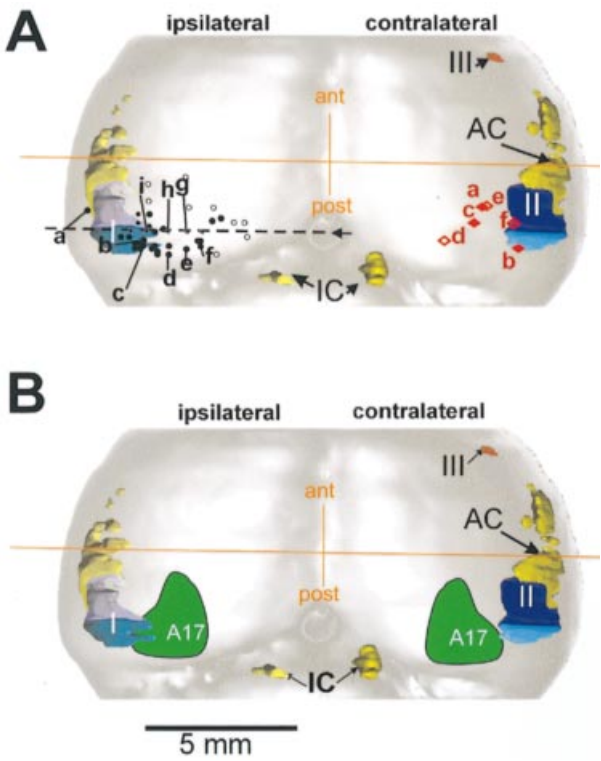



FIG. 7. Averaged 2DG-labelled brain and localization (A) of the microelectrode penetration sites in the occipital cortex and (B) of the delimitation of area 17. (A) Dorsal view of the cerebral hemispheres of an 'average brain'. The surface view of the hemispheres (in grey) and the 2DG labels (colour-coded) observed in four coronally cut brains of monaural mole rats were reconstructed and averaged (see Materials and methods). Color code as in Fig. 6. The horizontal orange line corresponds to the caudal border of the splenium of the corpus callosum, the vertical line to the interhemispheric sulcus. On the left, ipsilateral, hemisphere, we plotted the penetration sites where auditory evoked potentials were sampled. Responsive sites are shown by dark circles and nonresponsive sites by open circles. The dark arrow points to a dotted line that indicates the level of the coronal section illustrated in Fig. 8. The filled stars on that line indicate recording sites at that level identified by arrows in Fig. 8. Letters a–i refer to recording sites whose responses are illustrated in Fig. 9. On the right, contralateral, hemisphere, are indicated five penetration sites where unit responses to auditory stimuli were recorded and which are illustrated in Fig. 10. The closely spaced letters a and e represent two different units recorded at the same penetration site. (B) Localization of area 17 onto the occipital cortex of the 'average brain'. The surface view of the hemispheres (in grey) and the 2DG labels (colour-coded) are identical to that presented in A. Area 17, defined by its cyto- and myeloarchitecture (see text), is tentatively outlined and shaded in green. Note that the medial part of area I overlaps somehow with the presumptive area 17.

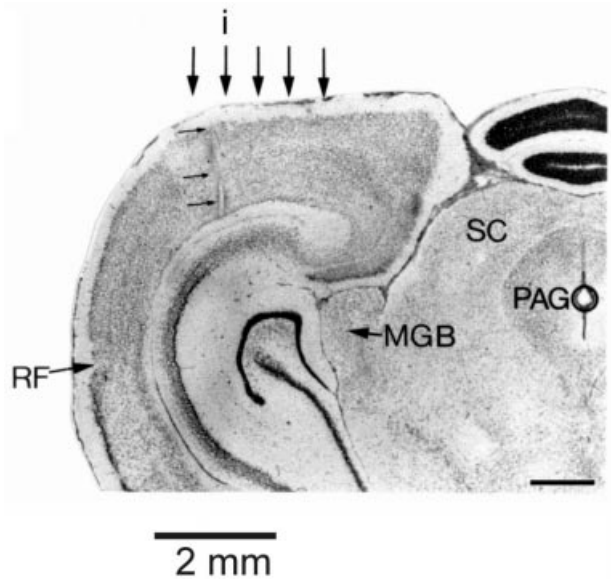



FIG. 8. Coronal Nissl-stained section at the level indicated by the dotted line in Fig. 7A. Vertical arrows represent recording sites indicated by stars in Fig. 7A. At the end of the recording session, lesions were made along the last recording track (horizontal arrows along the track labelled i).

range. In the cat's parastriate visual cortices (areas 18 and 19) many visual cells can also be driven by auditory stimuli (Morrel, 1972; Fishman & Michael, 1973). However, in this case auditory responses are very susceptible to anaesthesia, are of long latency and sustained in nature, and the cells are not tuned to frequency but seem to be tuned to the spatial location of the sound source which roughly matches their visual spatial tuning.

The functional role of auditory occipital regions of the mole rat in hearing is not yet known. It may be that they are enrolled in the processing of the spatial location of auditory signals and of seismic signals that blind mole rats use for intraspecific long-distance communication and that have been shown to be perceived by the auditory system (Rado *et al.*, 1989; Rado *et al.*, 1998).

The auditory-evoked 2DG accumulation in area III, within the parietal cortex, suggests a strong auditory input to this area. In rodents, auditory input to parietal cortex has already been reported: to the primary somatosensory cortex (representation of the hind limb; see Budinger *et al.*, 2000a) as well as to the secondary one (Carvell & Simons, 1986; Krubitzer *et al.*, 1986). However, no auditory input seems to reach the face representation area, at least in mice (Carvell & Simons, 1987). In this context the asymmetric 2DG labelling in the parietal cortex of unilaterally deafened mole rats (area III) is remarkable because this area corresponds seemingly (with the limited precision of our reconstruction method in mind) to the somatosensory representation of the jaws (Necker *et al.*, 1992; see Fig. 6). This correspondence is very interesting given the peculiar 'jaw-listening behaviour' of mole rats. We believe that the asymmetrical activation of area III in unilaterally deafened mole rats was caused by auditory stimulation, although we cannot entirely exclude the possibility that these animals behaved, during the 2DG experiment, in ways resulting in unilateral stimulation of the lower jaw. However, we never observed such asymmetrical behaviour during long-term observations of unilaterally and bilaterally deafened mole rats in the laboratory.

Further investigation is needed to explore the functional significance of the possibly bimodal activation of this cortical area by auditory and somatosensory signals.

Our spatial reconstruction of the auditory-activated occipital areas and responsive sites established their location caudal to the somatosensory representation described by Necker *et al.* (1992) (Fig. 6). The reconstruction of the cortical area activated by vibrissal stimulation, using the same frame of references, yielded a location entirely compatible with that somatosensory map and with its caudal expansion stressed by these authors.

Necker *et al.* (1992) were unable to record auditory (or visual) evoked responses caudal to the somatosensory representation. They

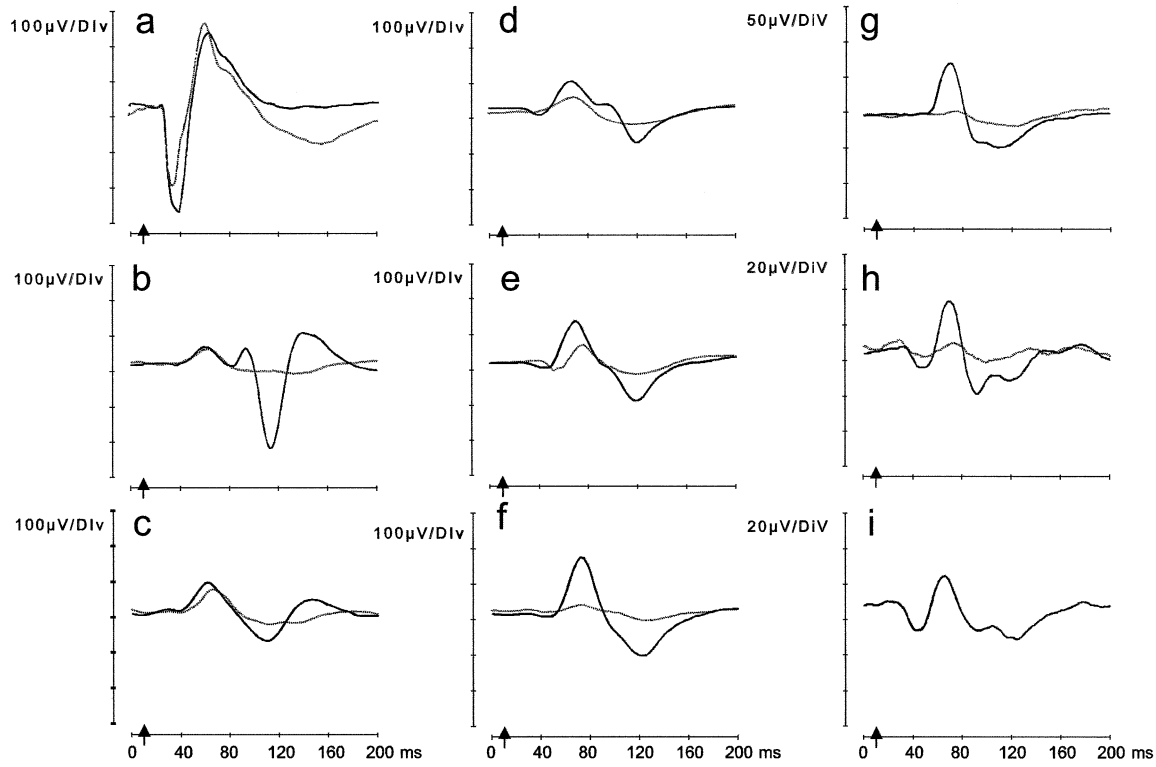



FIG. 9. Illustration of click-evoked field potentials recorded from the different sites (indicated in Fig. 7A) over the occipital cortex. For each site the response evoked by auditory clicks presented to the contralateral ear (solid heavy lines) and to the ipsilateral ear (light dotted lines) are shown. Timing of stimulation is indicated by the arrows at the bottom of each panel. Letters a–i represent recording sites designated in Fig. 7A. Note that the responses to clicks presented contralaterally are, in most cases, more prominent and somewhat more complex than those elicited by ipsilateral stimulation. Also note the different ordinate scales in a–i.

suggested that the auditory responses that we documented in a preliminary study (Heil *et al*., 1991) were in fact somatosensory responses elicited by the specules of the auditory transducers used in some of our early experiments. We consider this interpretation to be very unlikely, for the following reasons.

First, as demonstrated in this study, all the auditory-activated occipital regions are located caudal to the somatosensory representation, with a negligible overlap. Second, all 2DG experiments were conducted under free-field conditions, making a somatosensory stimulation of the ear region highly unlikely, particularly only on the side of the intact cochlea. Similarly, in later electrophysiological experiments we used earphones that were positioned close to the opening of the external auditory canal but not touching the skin. Finally, Necker *et al*. (1992) reported latencies of somatosensory responses from the face region of 8 ms, considerably shorter than the latencies of the auditory responses reported here from the occipital regions. We rather feel that Necker *et al*. (1992) may have missed auditory responses in the mole rat's occipital cortex. This appears conceivable, because they used clicks of an intensity of 76 dB SPL, measured at the head, which seems relatively low given that, in all but one of the animals studied, both ears were blocked by the ear bars of their stereotaxic apparatus. In the one animal, in which the contralateral ear bar was removed, they found a small auditory area caudolateral to the somatosensory head representation, i.e. in a region corresponding to what we believe are the posterior regions of the temporal auditory cortex (see Fig. 6). In that animal, auditory-responsive sites in the occipital cortex may still have been missed if that region was explored late in the course of the mapping experiment, given our observation of the increases in thresholds with time after induction of anaesthesia, and/or if only few sites were tested.

Thus, it seems that the conflicting interpretations regarding the organization of the mole rat's occipital cortex can be reconciled. Our data confirm the notion of Necker *et al*. (1992) that the somatosensory representation extends far into the occipital regions. Nevertheless, auditory regions also exist caudal to the somatosensory area, in addition to the auditory regions in the temporal cortex.

### *Is the occipital cortex of the blind mole rat homologueous to the visual cortex of sighted rodents?*

The issue here is whether these occipital auditory fields represent an expansion of the temporal auditory cortex into occipital regions at the expense of a classical visual cortex, which would thus be largely reduced in size, or alternatively whether the classical visual cortex is preserved but has been taken over by the auditory system. These alternatives are not mutually exclusive. Cooper *et al*. (1993b) described a relatively small area 17 in the mole rat's occipital cortex. Judging from the histological section they presented (their fig. 14), the proposed area 17 seems to be, to some extent, larger on the mediolateral axis than the one reconstructed by us, but also located somewhat medial to the auditory occipital area I described here. Therefore the definition of area 17 by Cooper *et al*. (1993b) and our reconstruction (Fig. 7B) appear to match well. Injections of retrograde tracers in this area 17 labelled cells in, among other thalamic structures, a small and narrow sheet-like nucleus dorsolateral to the posterior nucleus and nuclei posteromedialis and posterolateralis of

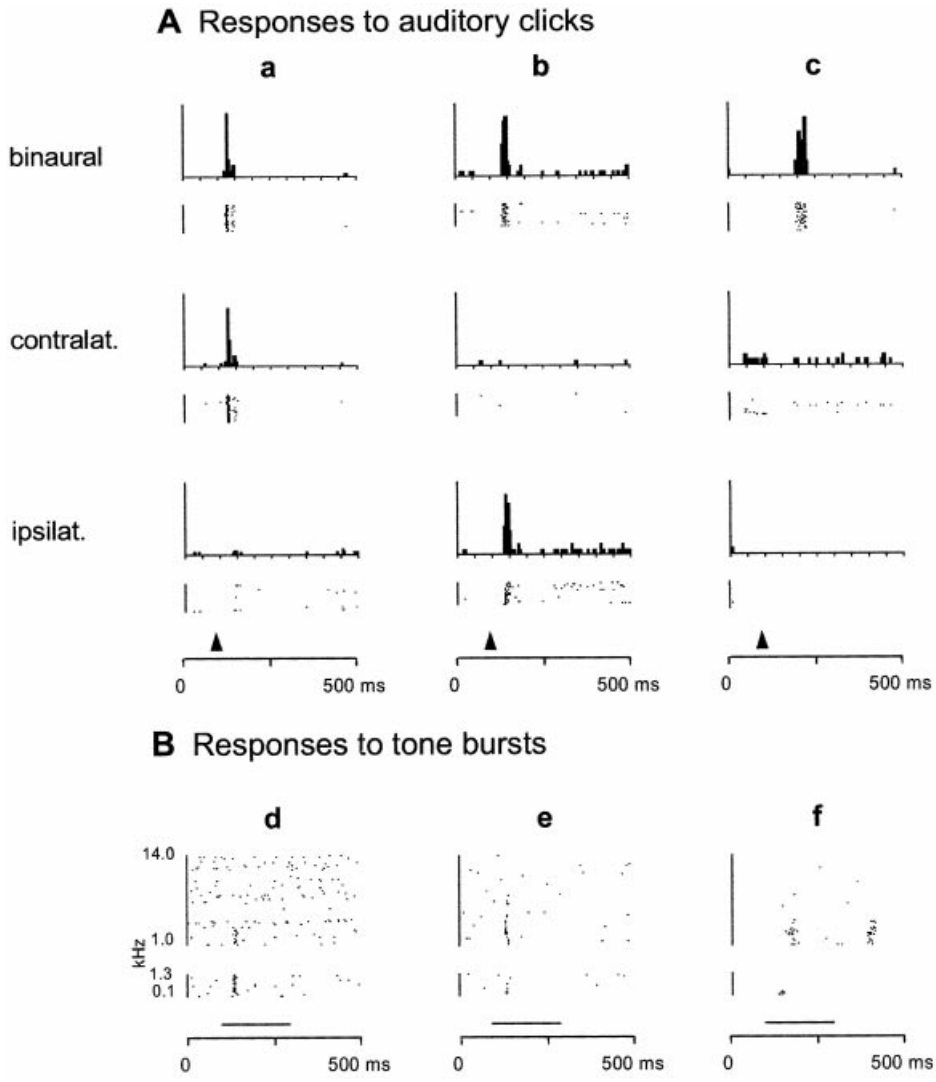



FIG. 10. Illustrations of single cell responses to auditory stimuli recorded from different sites in the occipital cortex (as indicated in Fig. 7A). (A) Responses (dot-raster displays and peristimulus–time histograms) of three different cells (a–c), located at three different sites (designated in Fig. 7A by the same letters and by filled symbols) to binaural, contralateral and ipsilateral presentation of auditory clicks. Timing of stimulation is indicated by the arrows at the bottom of each column. (B) Dot-raster displays representing the responses of three different cells (d–f), located at three different sites (designated in Fig. 7A by the same letters and by empty symbols), to contralateral presentation of pure tone bursts at a constant intensity of 80 dB SPL. Frequencies are represented vertically by 16 consecutive discrete steps (of ≈ 80Hz), from 0.1 to 1.3 kHz, in the lower set, and by 64 consecutive discrete steps (of ≈ 203 Hz), from 1.0 to 14.0 kHz in the upper set. The horizontal bar at the bottom of each display represents timing of stimulus presentation.

the thalamus. Because injections of tracer into the eye of the same animals led to anterograde, presumably terminal, labelling in that same structure, that nucleus is most probably the dLGB (Cooper *et al*., 1993b). Hence, the existence of a visual pathway from the minute retina via a tiny dLGB to an area 17 in the occipital cortex seems to favour the first alternative, although no visual activity could be recorded in this area 17 (Haim *et al*., 1983; Necker *et al*., 1992; and our own observation).

Our analysis of the cyto- and myeloarchitecture of occipital cortex suggests that area 17 overlaps marginally with the auditory-activated area I (Fig. 12). The electrophysiological survey, however, did reveal auditory-responsive sites within area 17 where no clear 2DG hotspot was found. This absence of correlation between the two mapping techniques can be observed where the specific auditory inputs constitute only a minority of the total input to a cortical area, or are weak. Then, auditory evoked 2DG uptake may be small, symmetical and difficult to detect. It should be noted that the auditory evoked potentials recorded in these medial occipital areas are very small, indeed, compared to those recorded more laterally, presumably in the posterior auditory fields (note the different scales used in Fig. 9).

The cytoarchitecture of area I is difficult to characterize. While it has the characteristics of area 17 in its medial portion, laterally it resembles more that of the adjacent auditory-activated area II which, in turn, closely resembles that of the visual cortical area 18a of the mouse or Oc2L of the rat (Caviness. (1975): Zilles, 1986). Injections of retrograde tracers into these auditory-activated cortical regions labelled neurons in, among other structures, a thalamic nucleus that we believe is the dLGB or a significant part of it (see Bronchti *et al*., 1991a; Heil *et al*., 1991; Doron & Wollberg, 1994). This structure lies

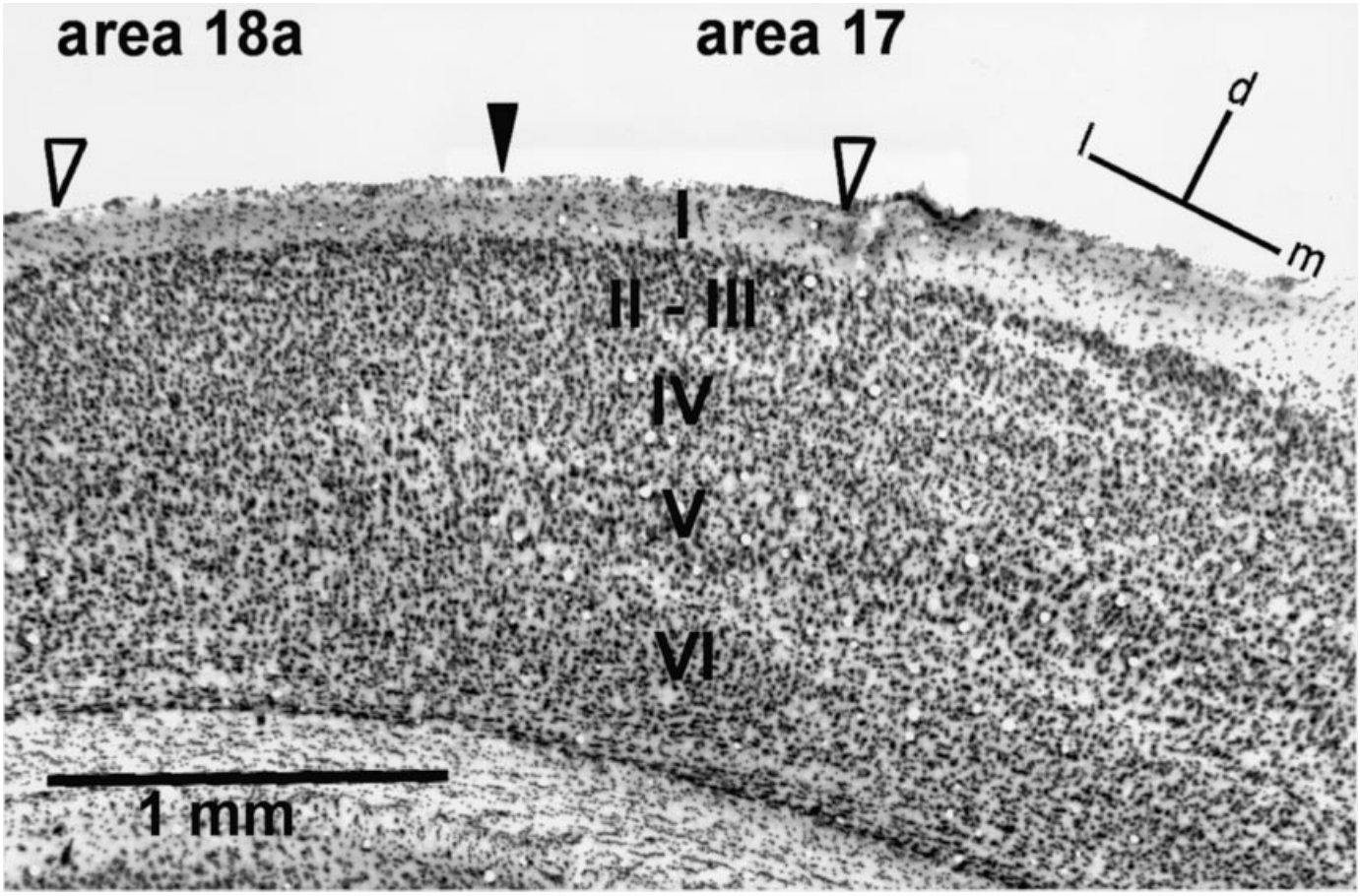



FIG. 11. Cytoarchitecture profile of area 17. Enlargement of Nissl-stained frontal sections through a cortical region of intense 2DG labelling corresponding to ipsilateral area I of a unilaterally deafened mole rat. The filled arrowhead points to the limit we assigned between area 17 and the lateral area 18a. The empty arrowheads delimit the extent of the 2DG hotspot (observed in the corresponding autoradiogram) which we defined as area I. Note the dense layer IV and the hypocellular layers Va and Vc in area 17 and the partial overlap between the functional area I and the cytoarchitectural area 17. d, dorsal; l, lateral; m, medial.

dorsolateral to the rostral MGB, separated from it by a conspicuous sheet of fibres, which is reflected in 2DG autoradiographs and in Nissl stains of transverse sections as a light band, and in myelin stain as a thick fibre bundle in contiguous positions within consecutive sections (Bronchti *et al*., 1989; see also fig. 3 in Rehkämper *et al*., 1994). This sheet is presumably the superior thalamic or the acoustic radiation (Paxinos & Watson, 1986) This presumed dLGB, which is of fair size but still smaller than that of sighted rodents, lies thus in a position corresponding to the caudal aspect of the dLGB in sighted rodents and appears to be rostrally continuous with the tiny dLGB identified by Cooper *et al*. (1993a, b) and by Rehkämper *et al*., 1994). It can also be easily identified in neonates where it receives retinal input (Bronchti *et al*., 1991b). Auditory input to this caudal part of dLGB originates from the central nucleus of the inferior colliculus (ICC) (Doron & Wollberg, 1994) as shown by injections of WGA–HRP (wheatgerm agglutinin–horseradish peroxidase) into, and restricted to, the dLGB. Furthermore, the same injections yielded retrogradely labelled cells in layers V and VI, and anterogradely labelled fibres in layers III and IV, of the ipsilateral occipital cortex, in a large area corresponding to area 17 and areas I and II as described here. In this context, it is noteworthy that a projection from the ICC to the dLGB has also been established in the mole *Mogera*, a subterranean insectivore (Kudo *et al*., 1997), and in a strain of anophthalmic mouse (Bronchti *et al*., 2000). If our interpretation of the histological material is correct, then our results strongly support the view of a takeover of a significant part of the thalamocortical visual system by the auditory system (Bronchti *et al*., 1989; Bronchti *et al*., 1991a; Heil *et al*., 1991; Doron & Wollberg, 1994).

Thus it appears that, in *Spalax*, the central visual pathways serving form and motion perception in sighted mammals are partly degenerated (Bronchti *et al*., 1991b; Cooper *et al*., 1993a; Cooper *et al*., 1993b) and partly taken over by the auditory system (Bronchti *et al*., 1989; Heil *et al*., 1991; Doron & Wollberg, 1994). In addition, at thalamic and cortical levels, the somatosensory representation is enlarged, mainly at the expense of the visual representation (Necker *et al*., 1992; Rehkämper *et al*., 1994; Mann *et al*., 1997)

How areas I and II evolved in the mole rat occipital cortex is unclear. It seems that the auditory input entering the dLGB from the inferior colliculus is relayed to the occipital cortex by an enlarged thalamocortical projection array (Doron & Wollberg, 1994). These projections activate both area 17 and lateral area 18a. Is this auditory-activated region of the occipital cortex a primary sensory area? We cannot answer the question yet. Only the medial part of area I, the one that overlaps with area 17, is as richly myelinated as would be expected in a primary sensory area.

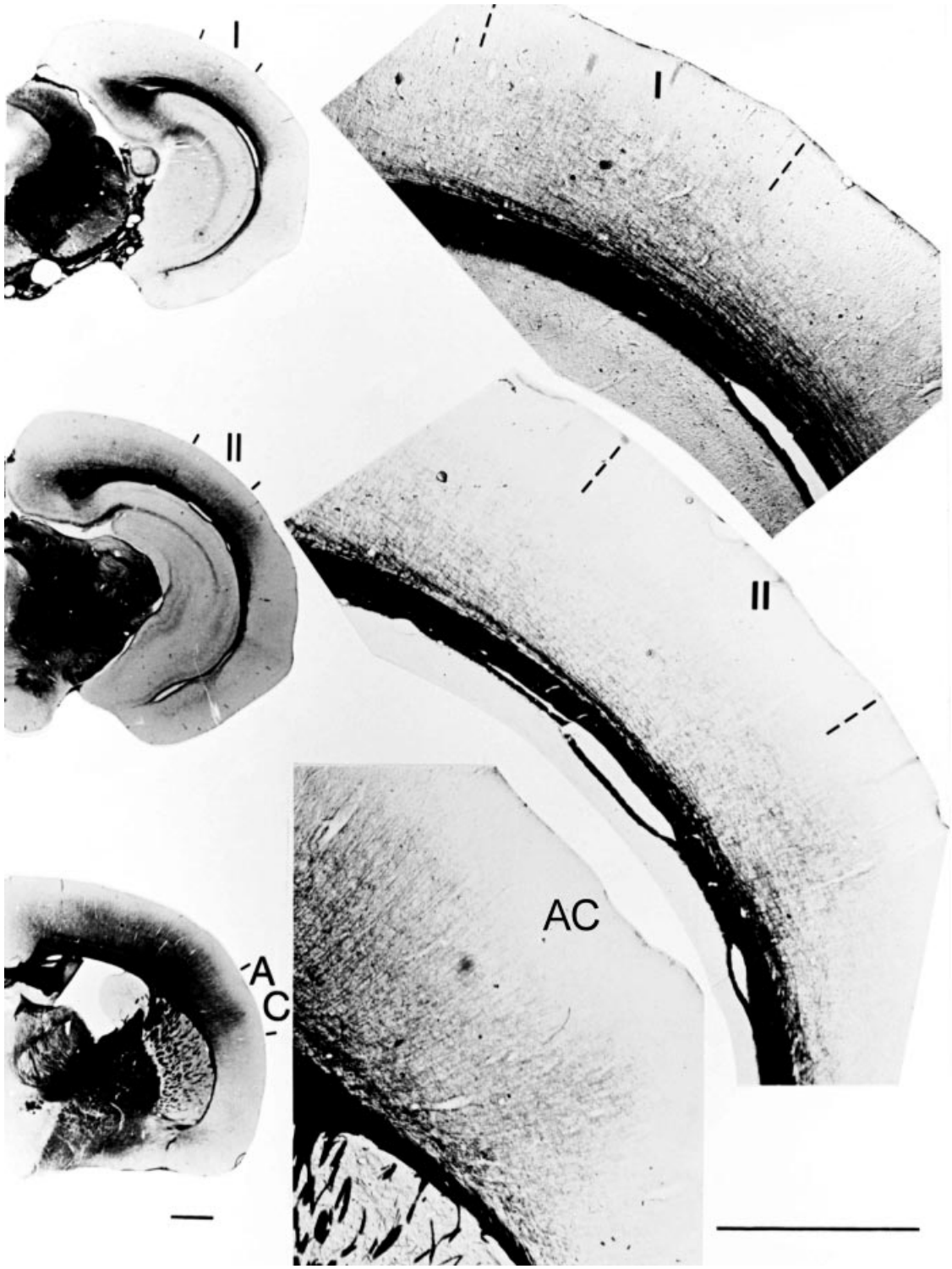



FIG. 12. Myeloarchitecture of different cortical areas as exposed by myelin stain of three selected coronal sections at low (left column) and high (right column) magnification. Note the relatively high myelination of area I and of AC as compared to area II. The delimitation of this densely myelinated area served for our tentative definition of area 17 in the mole rat. Scale bars, 1 mm.

A distinct cortical area homologous to area 17 is not unique for the blind mole rat. Such an area has also been suggested in congenitally anophthalmic or experimentally enucleated animals (Ruiz-Marcos & Valverde, 1970; Godement *et al*., 1979; Rhoades *et al*., 1984; Olavarria *et al*., 1987; Rakic, 1988; Yaka *et al*., 1999). Very interesting in this respect is the fact that the lateral aspect of area 17 in rats is the most sensitive one for functional changes following enucleation (Toldi *et al*., 1989). This is also the cortical region where a new cytoarchitectonic area emerges in monkeys enucleated during embryonic development (Rakic *et al*., 1991).

### *Functional significance of an auditory take-over of the visual system?*

Cross-modal re-routing of one sensory modality into targets of another sensory modality that has been surgically depleted of its original input has been demonstrated in several animal models (Frost, 1981; Frost & Metin, 1985; Sur & Garraghty, 1987; von Melchner *et al*., 2000). In most of these cases, the re-routing of the compensatory modality was enhanced by also surgically removing its own natural targets. For instance, it has been demonstrated that if the LGB and the superior colliculus, two principal visual nuclei, are removed in newborn Syrian hamsters, and an alternative terminal space is created by deafferentation of the somatosensory or auditory thalamic nuclei, the visual fibres that have lost their original target will form new connections in the abandoned thalamic nuclei (for a review see Frost, 1988). Moreover, visually driven cells, whose response properties resemble those typical of cells in the primary visual cortex of normal hamsters, were found in the somatosensory cortex of these neonatally operated animals. Likewise, visual projections have been forced into the auditory thalamus and auditory cortex in ferrets, and visual responses similar to those characteristic for visual cortex have been recorded in auditory cortex in such animals (e.g. Pallas *et al*., 1990; Sur *et al*., 1990; Pallas & Sur, 1993). Furthermore, the visual input directed to the auditory cortex can mediate visually driven behaviour (von Melchner *et al*., 2000). Changing the original afferent modality in these experimentally 'rewired' ferrets without altering the genuine thalamocortical projections profoundly modified cortical circuitry in the auditory cortex as well as callosal connectivity (Gao & Pallas, 1999; Pallas *et al*., 1999).

This experimental approach simulates only partly the situation found in congenitally blind animals such as the blind mole rat or anophthalmic mice (Asanuma & Stanfield, 1990). In both these cases there is a partial or complete deafferentation of the specific thalamic nucleus from its regular peripheral input. However, while in the experimentally impaired animals sensory deafferentation was accomplished surgically at birth, and the target of the compensating modality was also disturbed, in the naturally blind mole rat the retinofugal projections to the dLGB degenerate spontaneously within the first two weeks of postnatal development (Bronchti *et al*., 1991b), leaving the original auditory pathway intact. One major consequence of this difference is that in the blind mole rat the auditory-activated visual areas represent additional rather than alternative targets for the auditory projections. The fact that the connectivity between the dLGB and the 'classical' visual cortex, in the blind mole rat, remained intact, supports the notion that thalamocortical projections from specific thalamic nuclei to their cortical targets are apparently not affected by the deprivation of the pertinent peripheral sensory input (Kaiserman-Abramov *et al*., 1980; Guillery *et al*., 1985; Warton *et al*., 1988; Izraeli *et al*., 2002).

Activation of primary visual areas by other sensory modalities found in blind animal models is consistent with findings from blind human subjects that suggest that cortical visual areas in early-blinded humans are involved in the processing of auditory and/or somatosensory information (Sadato *et al*., 1996; Wanet-Defalque *et al*., 1988; Veraart *et al*., 1990; Uhl *et al*., 1991; Alho *et al*., 1993; Kujala *et al*., 1995). However, it is not known whether this activation involves intra or subcortical rewiring, or both. Is such neural reorganization in sensory impaired subjects somehow manifested behaviourally? Some recent findings suggest that cross-modal neuroplasticity might indeed account for certain superior tactile and/or hearing capabilities in blind animals and humans (Rauschecker & Kniepert, 1994; Lessard *et al*., 1998; Röder *et al*., 1999; Wollberg *et al*., 1999:Weeks *et al*., 2000).

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## Abbreviations

2DG, 2-deoxyglucose; AAF, anterior auditory field; AC, auditory cortex; AI, primary auditory field; CCA, connected-component analysis; dLGB, dorsal nucleus of the lateral geniculate body; IC, inferior colliculus; ICC, central nucleus of the inferior colliculus; LGB, lateral geniculate body; MGB, medial geniculate body; OD, optical density; rOD, relative optical density; S, symmetry index; SPL, sound pressure level.

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