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Experimentally Induced Visual Projections into Auditory Thalamus and Cortex

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SCIENCE

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Retinal cells have been induced to project into the medial geniculate nucleus, the principal auditory thalamic nucleus, in newborn ferrets by reduction of targets of retinal axons in one hemisphere and creation of alternative terminal space for these fibers in the auditory thalamus. Many cells in the medial geniculate nucleus are then visually driven, have large receptive fields, and receive input from retinal ganglion cells with small somata and slow conduction velocities. Visual cells with long conduction latencies and large contralateral receptive fields can also be recorded in primary auditory cortex. Some visual cells in auditory cortex are direction selective or have oriented receptive fields that resemble those of complex cells in primary visual cortex. Thus, functional visual projections can be routed into nonvisual structures in higher mammals, suggesting that the modality of a sensory thalamic nucleus or cortical area may be specified by its inputs during development.

WHAT IS INTRINSICALLY "VISUAL" about visual thalamus and cortex? Can visual projections be induced into nonvisual targets, and are these projections functional? The organization of the visual pathway in ferrets is similar to that in cats (*1*); the visual system of cats has been studied extensively both anatomically and physiologically. However, unlike cats, retinofugal projections in ferrets are very immature at birth (*2*); we reasoned that it might be possible to induce extensive plasticity in the retinothalamic pathway by surgery in neonatal ferrets.

Retinal targets were reduced in newborn ferret pups by ablating the superior colliculus and visual cortical areas 17 and 18 of one hemisphere (*3*) (Fig. 1). Ablating visual cortex causes the lateral geniculate nucleus (LGN) in the ipsilateral hemisphere to atrophy severely by retrograde degeneration. Concurrently, alternative target space for retinal afferents was created in the medial geniculate nucleus (MGN) by either ablating the inferior colliculus or sectioning fibers ascending to the MGN in the brachium of the inferior colliculus (*4, 5*).

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Experiments were done on 10 normal adult ferrets and 16 operated ferrets that were reared to adulthood. In five operated animals, intravitreal injections of anterograde tracers (*6*) revealed retinal projections to normal thalamic targets, including the surviving, shrunken LGN, as well as aberrant projections to auditory thalamic nuclei (Fig. 2). The new retinal projection zones included patches of the dorsal, medial, and ventral (or principal) divisions of the MGN, as well as parts of the lateral posterior nucleus and the posterior nuclear complex adjacent to the MGN. The retinal projections to the MGN complex occupied up to one-third of the volume of the MGN. We confirmed that the MGN in operated animals projected normally to auditory cortex (Fig. 1), both by the transneuronal label in auditory cortex after intraocular injections (*6*) and by the extensive retrograde labeling of cells in the MGN after restricted injections of horseradish peroxidase (HRP) or fluorescent retrograde tracers into primary auditory cortex (Fig. 2).

These experiments also indicated that the ipsilateral MGN is the major route for visual inputs to reach primary auditory cortex. Along with receiving major thalamic projections from the various divisions of the MGN (*7*), the primary auditory cortex in operated animals retained its connections with other auditory cortical areas. These included ipsilateral and contralateral connections with the second auditory area located lateral to primary auditory cortex and with areas on the ectosylvian gyrus located anterior, posterior, and ventral posterior to primary auditory cortex (*8*).

We next recorded responses of cells electrophysiologically from the MGN in operated animals (*9*) and compared visual responses there with responses from the surviving LGN in the same animals as well as from the LGN in normal animals. We studied the visual responses of single cells to various tests (*10*). We also tested the auditory responses of cells in the auditory thalamus with click or tone stimuli delivered through earphones.

In the LGN of normal animals, we recorded X, Y, and W cells (Fig. 3A); X and Y cells were found in the A laminae, and Y and

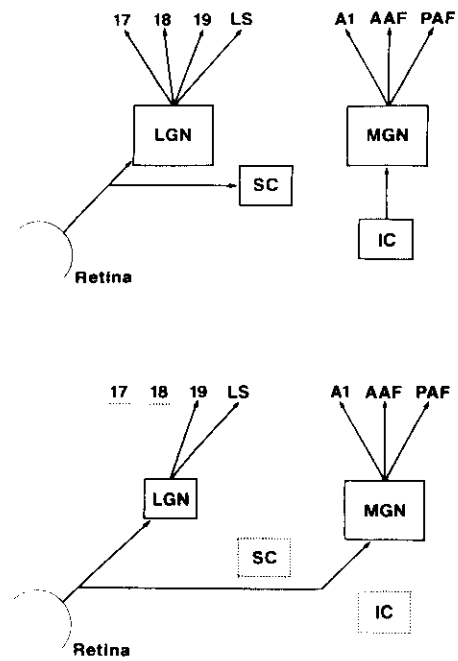

Fig. 1. The experimental design for induction of visual projections to the auditory system in ferrets. (**Top**) Projections in normal animals. The retina projects to LGN and superior colliculus (SC). The LGN projects to cortical areas 17 (primary visual cortex or striate cortex) and 18 as well as to other extrastriate areas including area 19 and the lateral suprasylvian (LS) cortex. In the auditory system, the inferior colliculus (IC) projects to the MGN. The ventral and the dorsal division of the MGN project heavily to primary auditory cortex (A1), as well as to other cortical areas including the anterior auditory field (AAF) and the posterior auditory field (PAF) in cortex (*29*). (**Bottom**) If cortical areas 17 and 18 are ablated in neonatal ferrets, the LGN atrophies severely by retrograde degeneration. Ablating the superior colliculus as well, and deafferenting the MGN by ablating the inferior colliculus or sectioning fibers ascending from it, causes the retina to project to the MGN and hence to auditory cortex.

Table 1. Visual cells recorded in primary auditory cortex of operated animals. Cells in primary auditory cortex were considered to receive retinal input if they were driven by electrical stimulation through electrodes implanted at the optic chiasm. They were then characterized by their responsiveness to visual stimuli.

Cell characteristic	Number of cells
Driven electrically from optic chiasm	57
Driven visually	38
Oriented receptive fields	6
Nonoriented receptive fields	23
Full-field flashes	9

W cells were found in the C laminae (*11*). In the LGN of operated animals, we recorded almost exclusively Y cells in the A laminae (Fig. 3B). We ascribe the loss of X cells in the LGN to the retrograde degeneration of geniculate X cells after ablation of visual cortex. A similar result has been shown in cats (*12*); in cats, neonatal visual cortical ablation also leads to transneuronal retrograde loss of X cells in the retina (*13*), and we have confirmed a reduction in medium-sized retinal ganglion cells in operated ferrets (*14*).

In the MGN of operated animals, we recorded cells with long latencies to optic chiasm stimulation (Fig. 3C). The conduction latencies of cells in the MGN of operated animals (range of latencies 2.8 to 11.0 ms, mean latency 4.8 ms, for 94 cells in five animals) were significantly longer than the latencies of X and Y cells in the LGN of normal animals (range of latencies 1.5 to 3.0 ms, mean latency 2.0 ms, for 101 cells in five animals; $P < 0.005$, Mann-Whitney U test, for a comparison of mean latencies in individual normal and operated animals). The visual responses of cells in the MGN were often variable or "sluggish" (*15*); cells responded best to large, flashing, or moving spots of light. Receptive fields were large, with diameters that were two to five times the diameters of normal LGN X cell receptive fields and up to twice the diameter of LGN Y cell receptive fields at similar eccentricities. Neurons dorsal in the MGN represented the upper visual field, neurons located ventrally represented lower visual field, neurons located medially represented central visual field, and those located laterally represented peripheral field. Receptive fields were on, off, or on-off center and circular. Visually driven cells were not orientation selective, although 2 of 32 visual units were direction selective (*16*). We used HRP to retrogradely fill retinal ganglion cells that projected to the LGN or superior colliculus in normal animals and to the LGN or MGN in operated animals (*17*). In normal adult ferrets, retinal ganglion cells include large-sized α (Y-like) cells that project to the LGN and superior colliculus, medium-sized β (X-like) cells that project mainly to the LGN, and a heterogeneous population of small and medium-sized (W-like) cells that project to the LGN and to the superior colliculus (*18*). In operated ferrets, the projection to the MGN arose mainly from the small retinal ganglion cells with heterogeneous morphologies (Fig. 3D). Our physiological and anatomical results thus suggest that the retinal ganglion cells that project to the MGN in operated animals belong to the W class. However, we cannot rule out the possibility that at least some cells that give rise to the aberrant projection are X or Y cells that fail to develop normally.

We also recorded from single units in primary auditory cortex of operated animals to determine their visual response features. Visual responses were strongest in the middle layers, at depths of 600 to 900 μm. In primary auditory cortex, as in the MGN, cells had long latencies to optic chiasm stimulation; the latencies ranged from 5.5 to 17.0 ms, with a mean latency of 9.0 ms (57 cells recorded in six operated animals). For comparison, latencies to optic chiasm stimulation in primary visual cortex of normal animals, which is dominated by the moderate- and fast-conducting X and Y pathways through the LGN (*1*), ranged from 2.0 to 6.5 ms, with a mean latency of 4.2 ms (63 cells recorded in four normal animals). The latencies in normal animals were significantly shorter than those in operated animals ($P < 0.005$, Mann-Whitney U test, for a comparison of mean latencies in individual animals). Cells in primary auditory cortex that were driven by visual stimulation formed a subset of the cells that were driven by electrical stimulation of the optic chiasm (Table 1). Visual cells in auditory cortex had large receptive fields and preferred slowly flashing or moving large spots or bars. As in the MGN, receptive fields were confined to the contralateral hemifield (*19*). About 25% of the cells that we could drive visually (10 of 38 units) showed direction selectivity. About 20% of cells showed orientation selectivity (Table 1) (Fig. 4) (*20*). All of the oriented cells had coextensive on and off

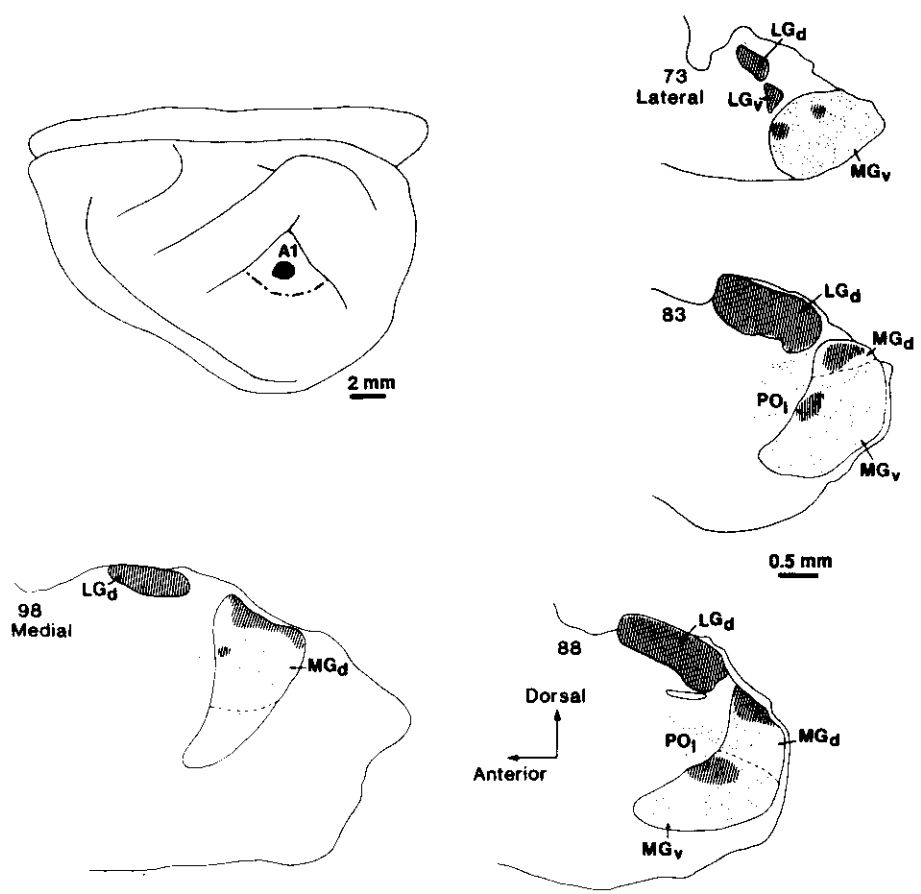

Fig. 2. Experimentally induced retinal projections (hatched areas) to the auditory thalamus and the connections of auditory thalamus with auditory cortex. The eye contralateral to the operated hemisphere projects to the surviving dorsal LGN (LG_d) and ventral LGN (LG_v) as well as to patches within the dorsal and ventral divisions of the MGN (MG_d and MG_v, respectively). Numbered parasagittal sections of the thalamus are shown. In the same animal, an injection of HRP in primary auditory cortex (A1) (the injection site is shown at top left) fills cells (indicated by dots) retrogradely in MG_v, MG_d, and the lateral division of the posterior complex (PO_l). Many cells in MG_d and MG_v overlie the retinal projection zone.

zones and responded to light onset and offset or to light and dark edges, and we classified them as complex (*21*, *22*).

We could drive few neurons in the MGN or primary auditory cortex of the operated hemisphere with acoustic stimuli. This result was not unexpected because we had deafferented the MGN, but it confirmed that severed axons did not regenerate from the inferior colliculus to the MGN, at least not in large numbers. We could reliably elicit auditory responses from the MGN and primary auditory cortex in the unoperated hemisphere. We could not elicit responses to either electrical stimulation of the optic tract or visual field stimulation from cells in primary auditory cortex in normal animals (n = 48 single and multiple units) (*23*).

These results demonstrate that retinal projections can be induced to grow into nonvisual thalamus in ferrets and that these projections can impart visual function (that is, visual driving and discernible receptive field properties) to cells in nonvisual thala-

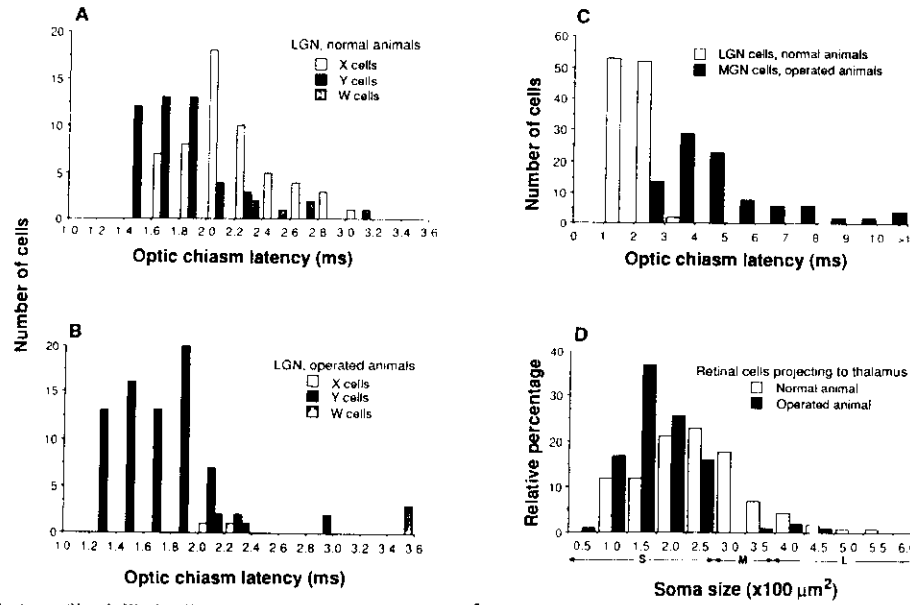

Fig. 3. Electrophysiological results from the thalamus of operated and normal animals and anatomical labeling of retinal ganglion cells that provide input to the thalamus in these animals. (**A**) The distribution of the latencies of firing, after electrical stimulation of the optic chiasm, of X, Y, and W cells in the LGN of normal animals. The histogram includes 107 cells pooled from five animals. X and Y cells are found in the A laminae, whereas the C laminae contain Y and W cells (*11*). (**B**) The LGN of operated animals contains Y cells (found in the A and C laminae), along with W cells (found in the C laminae), but very few X cells. Data are from 81 cells pooled from five animals. (**C**) Cells in the MGN of operated animals (94 cells in five animals) have long latencies to optic chiasm stimulation compared to cells in the LGN of normal animals [same data as in (A)]. (**D**) Histogram of soma sizes of retinal ganglion cells filled retrogradely from an HRP injection in the thalamus of a normal animal and an operated animal. The injection in the normal animal was centered on the LGN, and the injection in the operated animal was centered on the MGN. Each bar in the histogram represents the ganglion cells in a given size range as a percentage of the total population of backfilled cells. Retinal input to the thalamus in normal ferrets (*18*) arises from α or Y-like cells [these are, in general, large (L) cells with soma sizes of 400 μm² and larger), β or X-like cells [generally medium (M)-sized cells with soma sizes between 300 and 400 μm²), and a heterogeneous population of W-like cells [generally small (S) cells with soma sizes smaller than 300 μm², although this class can include medium-sized cells as well]. In operated ferrets, the cells that project to the MGN lie mainly in the small size range.

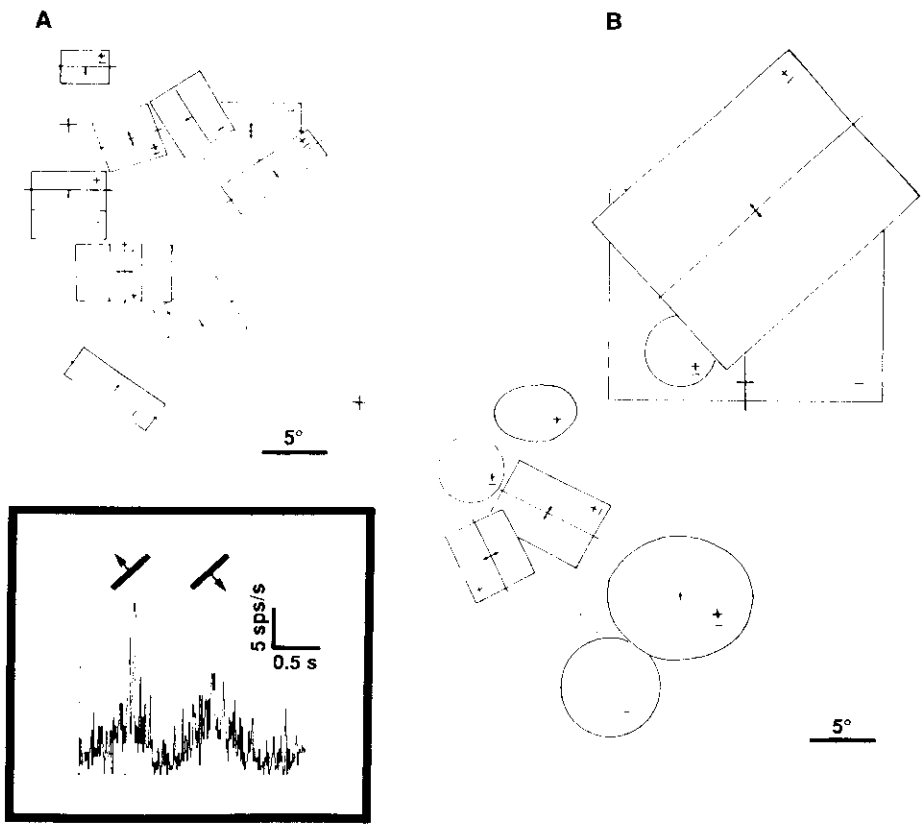

Fig. 4. Receptive fields of visual cells in primary auditory cortex of an operated animal with visual projections induced into the auditory system and comparison with receptive fields in primary visual cortex of a normal animal. Cells were classified as nonoriented or oriented simple or complex according to the criteria of Hubel and Wiesel (*21*). Simple cells have oriented fields with separate on (+) and off (−) zones, whereas complex cells have oriented fields usually with coextensive on and off zones. (**A**) Cells recorded in area 17 of a normal animal. Receptive field locations shifted progressively higher in the visual field as recording locations moved from dorsal to ventral in area 17, consistent with the map of visual space in area 17 in ferrets (*30*). The cross denotes the location of the area centralis. Small arrows within the receptive field denote the direction of stimulus movement yielding maximal response. Oriented line within each receptive field extending beyond receptive field edges denotes lack of end-stopping; lines that terminate at receptive field edges indicate end-stopped fields. (**B**) In primary auditory cortex of an operated ferret, visual cells had either nonoriented (circular) or oriented (rectangular) receptive fields. The oriented fields were complex-like. Receptive fields moved from dorsal to ventral in the visual field as recording locations moved from posteromedial to anterolateral in auditory cortex. (Inset) Peristimulus time histogram of a visual cell in primary auditory cortex responding to a bar sweeping across the receptive field at the orientation and directions indicated above the histogram. Bar width, 1°; bar length, 20°; velocity, 5°/s; 50 stimulus sweeps; sps/s, spikes per second.

mus and cortex. We suggest that, at least early in development, the modality of sensory thalamus or cortex can be specified by its inputs. Unlike rodents that have transient retinal projections to nonvisual thalamus that can be made permanent (*24*), in newborn ferrets the retina does not project to auditory thalamus (*25*). The novel retinal projections to the auditory thalamus thus represent sprouting from retinofugal fibers. If temporal factors play a role in the plasticity we describe, those retinal ganglion cells that have yet to establish stable thalamic or midbrain connections at the time of the lesions—including the smaller retinal ganglion cells that are generated last in the retina (*26*)—would be the most likely to innervate novel targets. Thus, surgery performed even earlier in development might induce more ganglion cells and perhaps other ganglion cell classes to reroute their axons as well. Alternatively, only certain retinal axons, intrinsically different from others, may be able to recognize cues in the denervated MGN and sprout into the nucleus.

Apart from the retinal cell classes that are involved in novel projections to the auditory system, our experiments provide a direct comparison of visual responses of neurons in the normal visual pathway with those induced into a pathway through nonvisual thalamus to cortex ~~resembling those in primary visual cortex~~. Ideally, an evaluation of visual response features in primary auditory cortex and in normal striate cortex, for example, should involve cells that receive input from the same class of retinal ganglion cell in both structures (*27*). Still, our experiments suggest that some of the transformations on visual input performed in visual structures such as primary visual cortex in normal animals are possible as well in the primary auditory cortex in operated animals. One possibility consistent with our results is that visual inputs induce the development of specific intrinsic connections in primary auditory cortex resembling those in primary visual cortex. An alternative possibility is that intrinsic processing in primary auditory cortex may be similar in certain respects to that in primary visual cortex. This similarity might allow auditory cortex to process visual information; indeed, a parsimonious explanation of our results is that primary areas of sensory neocortex perform certain similar, stereotypical operations on input regardless of modality (*28*).

REFERENCES AND NOTES

1. Major features of organization of the retinogeniculate and geniculocortical pathways in mustelids (for example, ferrets and mink), which are carnivores like cats, have been described [R. W. Guillery and M. D. Oberdorfer, *J. Comp. Neurol.* **176**, 515 (1977); M. P. Stryker and K. R. Zahs, *J. Neurosci.* **3**, 1943 (1983); S. K. McConnell and S. LeVay, *J. Comp. Neurol.* **250**, 109 (1986); S. LeVay, S. K. McConnell, M. B. Luskin, *ibid.* **257**, 422 (1987)]. A review of the visual pathway in cats is given by S. M. Sherman and P. D. Spear [*Physiol. Rev.* **62**, 738 (1982)].
2. Ferrets are born after 41 days of gestation compared to 64 days for cats. At birth, the development of the retinogeniculate pathway in ferrets [D. C. Linden, R. W. Guillery, J. Cucchiaro, *J. Comp. Neurol.* **203**, 189 (1981)] resembles that in cats at about embryonic day 41 [C. J. Shatz, *J. Neurosci.* **3**, 482 (1983); D. W. Sretavan and C. J. Shatz, *ibid.* **6**, 234 (1986)], and subsequent retinofugal development in ferrets matches that in cats almost on a day-by-day basis.
3. Our basic surgical procedure is modified from that described for hamsters by G. E. Schneider [*Brain Behav. Evol.* **8**, 73 (1973)]; see also D. O. Frost [*J. Comp. Neurol.* **203**, 227 (1981)].
4. On the day of birth, ferret pups were anesthetized by hypothermia. An incision was made to expose the skull, and a flap of bone over visual cortex and superior colliculus of one hemisphere was removed. Visual cortex corresponding to areas 17 and 18 and the superior colliculus were then ablated unilaterally by cautery. In some animals, the inferior colliculus was ablated; in other animals, ascending auditory fibers in the brachium of the inferior colliculus were sectioned at the level of the midsuperior colliculus by inserting a blade coronally in the lateral portion of the midbrain. The scalp incision was sutured, and pups were revived and returned to the litter for rearing to adulthood.
5. In control experiments, we have examined the necessary and sufficient conditions for inducing retinal projections to auditory thalamus. Retinal fibers do not enter the MGN unless it is deafferented. Ablating the superior colliculus alone, along with deafferenting the MGN, causes a weak projection to the MGN. The projections are much heavier if visual cortex is ablated as well. We have been unable to induce retinal projections into nonvisual thalamic structures in cats by neonatal surgery, perhaps because by the time of birth, the retinal axons of cats have already grown into their target visual structures.
6. Adult ferrets were anesthetized with 2 to 3% halothane or with a mixture of ketamine (30 mg/kg) and xylazine (2 mg/kg). Intraocular injections were made with 15 to 25 μl of either wheat germ agglutinin conjugated to HRP (2%) or [^{35}S]methionine (500 μCi) dissolved in saline. Survival times ranged from one to several days. Animals were then deeply anesthetized and perfused intracardially with saline followed by a mixture of 1% paraformaldehyde and 2% glutaraldehyde. Frozen sections (50 μm) were cut in the parasagittal or coronal plane and processed for visualization of HRP [M.-M. Mesulam, *J. Histochem. Cytochem.* **26**, 106 (1978); J. C. Adams, *Neuroscience* **2**, 141 (1977)] or for autoradiography.
7. R. A. Andersen, P. L. Knight, M. M. Merzenich, *J. Comp. Neurol.* **194**, 663 (1980); J. C. Middlebrooks and J. M. Zook, *J. Neurosci.* **3**, 203 (1983).
8. S. L. Pallas *et al.*, *Neurosci. Abstr.* **14**, 460 (1988).
9. Physiological experiments were done on 12 operated ferrets and 8 normal ferrets. Animals were anesthetized, paralyzed, and artificially respired. The eyes were refracted and focused on a tangent screen 114 cm in front of the animal. Stimulating electrodes were placed across the optic chiasm. Cells in the LGN and MGN, or in visual and auditory cortex, of normal and operated animals were recorded with glass micropipettes or parylene-insulated tungsten microelectrodes. Electrolytic lesions were made during recording with metal electrodes, and these lesions as well as electrode tracks were reconstructed and compared with architectonic regions to locate recording sites within the LGN and MGN, or within primary visual and primary auditory cortex.
10. Parameters we studied included receptive field size, latency to optic chiasm stimulation, linearity of spatial summation within the receptive field, time course of response to a stationary stimulus, and response to a fast-moving disk of contrast appropriate for the surround. These tests have been used to classify W, X, and Y cells in the cat LGN [C. Enroth-Cugell and J. G. Robson, *J. Physiol. (London)* **187**, 516 (1966); S. Hochstein and R. M. Shapley, *ibid.* **262**, 237 (1976), and M. Sur and S. M. Sherman; *J. Neurophysiol.* **47**, 869 (1982)]. We also studied the responses of cells to stationary flashed bars at different orientations and to spots moving in different directions at different velocities. For 19 visually responsive MGN cells, peristimulus time histograms were generated in response to a drifting or counterphasing sine-wave grating or a bar moving at different orientations and velocities.
11. M. Esguerra, P. E. Garraghty, G. S. Russo, M. Sur, *Neurosci. Abstr.* **12**, 10 (1986).
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14. M. Sur, A. W. Roe, P. E. Garraghty, *Neurosci. Abstr.* **13**, 590 (1987).
15. B. G. Cleland and W. R. Levick, *J. Physiol. (London)* **240**, 421 (1974).
16. None of 12 X and 16 Y cells in the LGN of normal animals and 19 Y cells in the LGN of operated animals showed orientation or direction selectivity.
17. HRP (30% in saline) was iontophoresed into physiologically identified sites in the LGN, superior colliculus, or MGN. After 24 to 48 hours of survival, animals were perfused with 1% paraformaldehyde and 2% glutaraldehyde. The retinas were dissected, reacted with *O*-dianisidine [J. S. De Olmos, *Exp. Brain Res.* **29**, 541 (1977)], and flat-mounted on slides. Retrogradely filled retinal ganglion cells were examined under a ×50 objective, and their soma areas were measured.
18. D. J. Vitek, J. D. Schall, A. G. Leventhal, *J. Comp. Neurol.* **241**, 1 (1985); A. W. Roe, P. E. Garraghty, M. Sur, *Neurosci. Abstr.* **13**, 1023 (1987). Central projections of retinal ganglion cells in ferrets are similar to those in cats [A. G. Leventhal, R. W. Rodieck, B. Dreher, *J. Comp. Neurol.* **237**, 216 (1985); L. R. Stanford, *J. Neurophysiol.* **57**, 218 (1987)].
19. This finding is consistent with the fact that there are no visual inputs into primary auditory cortex through the corpus callosum from visual areas in the contralateral hemisphere.
20. For each neuron showing orientation or direction selectivity, we defined the width of orientation or direction tuning as the range of orientations or movement directions to which the cell responded. Six visual units in primary auditory cortex that were orientation selective (Table 1) had orientation tuning widths of 60° to 120° (mean, 94°), and ten units that were direction selective had direction tuning widths of 60° to 180° (mean, 125°). In comparison, cells in striate cortex of three normal animals had orientation tuning widths of 30° to 90° (mean, 59°; $n = 27$) and direction tuning widths of 30° to 120° (mean, 85°; $n = 19$). No orientation-selective neuron in primary auditory cortex showed end-inhibition, but 7 of 27 units in normal striate cortex were end-inhibited (see also Fig. 4).
21. D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **160**, 106 (1962).
22. C. D. Gilbert, *ibid.* **268**, 391 (1977).
23. This finding confirms experiments on localization in the cat cortex, including early experiments in which visual- and auditory-evoked potentials were recorded from the cortical surface [W. H. Marshall, S. A. Talbot, H. W. Ades, *J. Neurophysiol.* **6**, 1 (1943); R. F. Thompson, R. H. Johnson, J. J. Hoopes, *ibid.* **26**, 343 (1963)], that have distinguished primary auditory cortex as a region where only auditory and no visual responses can be recorded.
24. D. O. Frost, *J. Comp. Neurol.* **252**, 95 (1986); ——— and C. Metin, *Nature* **317**, 162 (1985).
25. D. C. Linden, R. W. Guillery, J. Cucchiaro, in (*2*); J. Hahm and M. Sur, *Neurosci. Abstr.* **14**, 460 (1988).
26. C. Walsh, E. H. Polley, T. L. Hickey, R. W. Guillery, *Nature* **302**, 611 (1983); C. Walsh and R. W. Guillery, *J. Neurosci.* **5**, 3061 (1985).
27. Whereas the visual projections through the MGN to primary auditory cortex in operated animals appear to arise chiefly from retinal W cells, visual inputs to striate cortex in normal animals arise from retinal X and Y as well as W cells. Although the literature on response properties of cells in normal visual cortex is extensive, little of it derives from cells with pure W cell input; however, see B. Dreher, A. G. Leventhal, and P. T. Hale [*J. Neurophysiol.* **44**, 804 (1980)].
28. Several lines of evidence support such a conclusion.

(i) Intrinsic interlaminar connections described for cat striate cortex [C. D. Gilbert and T. N. Wiesel, *Nature* **280**, 120 (1979); D. Ferster and S. Lindstrom, *J. Physiol. (London)* **342**, 181 (1983)] share fundamental similarities with those described for cat primary auditory cortex [A. Mitani *et al.*, *J. Comp. Neurol.* **235**, 430 (1985)]. (ii) Direction-selective neurons (responding to the direction and rate of sound frequency modulation) have been noted in primary auditory cortex [I. C. Whitfield and E. F. Evans, *J. Neurophysiol.* **28**, 655 (1965); J. R. Mendelson and M. S. Cynader, *Brain Res.* **327**, 331 (1985)]. In the somatosensory cortex, direction- and orientation-selective neurons analogous to those in striate cortex have been described [J. Hyvarinen and A. Poranen, *J. Physiol. (London)* **283**, 523 (1978); S. Warren, A. Hamalainen, E. P. Gardner, *J. Neurophysiol.* **56**, 598 (1986)]. A more general discussion of common aspects of processing in sensory cortex is by V. B. Mountcastle [*The Mindful Brain*, G. M. Edelman and V. B. Mountcastle, Eds. (MIT Press, Cambridge, 1978), pp. 7–50]. (iii) In our experiments, lesions are used to route retinal projections into the auditory thalamus, and the extrinsic and intrinsic connections of auditory cortex are not altered, at least directly. Other experiments provide evidence for target-controlled differentiation of synaptic structure during development [G. Campbell and D. O. Frost, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 6929 (1987); P. Rakic, *Science* **241**, 170 (1988)], suggesting that the neuropil of primary auditory cortex in operated animals would resemble that in normal animals. Thus the fact that auditory cortex in operated animals can process visual information in a manner similar to normal visual cortex implies that at least some aspects of intrinsic processing are similar in visual and auditory cortex.

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A Map of Visual Space Induced in Primary Auditory Cortex

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A Map of Visual Space Induced in Primary Auditory Cortex

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Maps of sensory surfaces are a fundamental feature of sensory cortical areas of the brain. The relative roles of afferents and targets in forming neocortical maps in higher mammals can be examined in ferrets in which retinal inputs are directed into the auditory pathway. In these animals, the primary auditory cortex contains a systematic representation of the retina (and of visual space) rather than a representation of the cochlea (and of sound frequency). A representation of a two-dimensional sensory epithelium, the retina, in cortex that normally represents a one-dimensional epithelium, the cochlea, suggests that the same cortical area can support different types of maps. Topography in the visual map arises both from thalamocortical projections that are characteristic of the auditory pathway and from patterns of retinal activity that provide the input to the map.

THE MECHANISMS BY WHICH SENSORY maps form in the neocortex remain an outstanding question in cortical development. There is evidence that both the cortical target tissue (*1*) and sensory information from peripheral receptors (*2*) are important in the mapping process. We have addressed the question by using a preparation in which fibers from the retina are directed into the auditory pathway in ferrets. In particular, we asked whether primary auditory cortex, which normally contains a representation of the cochlea, would now contain a systematic map of the retina and of visual space. We reasoned that a map of the visual field in primary auditory cortex, if it were to exist, would also provide important clues to how cortical targets and sensory inputs contribute to generating maps of sensory surfaces in the cortex.

To route visual projections to auditory cortex, the retina is deprived of its two major targets by surgical lesions in neonatal ferret kits. One target, the superior colliculus, is ablated directly, while the other target, the lateral geniculate nucleus (LGN), atrophies severely by retrograde degeneration after ablation of visual cortex. Concurrently, ascending auditory fibers to the medial geniculate nucleus (MGN), the principal auditory thalamic nucleus, are sectioned in the brachium of the inferior colliculus. Retinal afferents then project into the deafferented MGN (*3*); in lesioned animals reared to adulthood, neurons with well-defined visual responses can be recorded in this nucleus and from its main cortical target, the primary auditory cortex (*4*).

We have now examined the map of the visual field induced in primary auditory cortex in lesioned animals. Adult ferrets ($n = 7$), operated on at birth as described above, were prepared for electrophysiological recording (*5*). A grid of electrode penetrations was made in primary auditory cortex. We plotted receptive fields of visual cells recorded in cortex on a tangent screen using flashing or moving spots or bars of light. We identified recording sites as lying within primary auditory cortex by matching lesions made during recording with borders defined histologically (*6*).

Cortical recording sites and corresponding visual receptive field locations from an adult ferret in which retinal projections were induced into the auditory pathway are shown in Fig. 1. Receptive fields close to the vertical midline of the visual field are represented at the medial edge of primary auditory cortex (Fig. 1, A to C; receptive fields 1 and 2), and more peripheral parts of the visual field lie progressively laterally in cortex. Several receptive field sequences (Fig. 1, B and C) show that lower visual field elevations are represented posteriorly in cortex, and receptive fields move upward in elevation as recording sites move anteriorly across cortex.

We have quantified several aspects of the map. The map is retinotopic overall, although there is some variability in receptive field location (*7*). Azimuths increase systematically with mediolateral distance on the cortex (Pearson's coefficient of correlation, $r = 0.74$, $P < 0.01$), while elevations increase from posterior to anterior ($r = 0.46$, $P < 0.05$). Mapping indices (*7*) that compare actual locations with theoretical ones for a perfectly retinotopic map indicate that azimuths are mapped more precisely than elevations (*8*). Magnification (*9*) is relatively constant across the map (Fig. 1D), suggesting a linear mapping of the retina on cortex (*10*).

The map shown in Fig. 1 is an example of the maps we have recorded in primary auditory cortex in four lesioned animals. The representation of azimuth is stereotypical in all maps, increasing from medial to lateral in cortex. Furthermore, the representation of azimuth is consistently more precise than the representation of elevation (*11*). Indeed, the polarity of the elevation representation can reverse in some animals so that elevations either increase from posterior to anterior in cortex (as shown in Fig. 1; three animals) or from anterior to posterior (data not shown; one animal).

We regard these observations as significant for understanding how sensory maps form in the cortex. Our results demonstrate that the form of the map is not an intrinsic property of the cortex and that a cortical area can come to support different types of maps. In normal ferrets, primary auditory cortex contains a representation of the cochlea (*12*), with low sound frequencies represented laterally and high frequencies medially in cortex; the mediolateral dimension thus constitutes the variable-frequency axis in cortex. Neurons along the anteroposterior dimension in primary auditory cortex all represent the same sound frequency and constitute the isofrequency axis (*13*). In lesioned ferrets, a systematic representation of the retina and of visual space occupies both the mediolateral and anteroposterior dimensions of cortex. Thus, cortex that normally represents a one-dimensional (1-D) sensory epithelium (the cochlea) can, after early developmental manipulations, represent topographically a two-dimensional (2-D) epithelium (the retina).

The mechanisms by which topography is

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established in the dimensions of azimuth and elevation of the visual map are likely to be different. The normal pattern of projections from the MGN to primary auditory cortex (*14*) is highly topographic along the variable frequency axis but rather convergent and divergent [within the excitatory-excitatory (EE) and excitatory-inhibitory (EI) systems (*15*)] along the isofrequency axis (Fig. 2). Thus, in lesioned animals, the existing thalamocortical organization along the mediolateral or "variable frequency" dimension of cortex would lead to topography along the azimuthal axis of the visual map (*16*). However, along the anteroposterior or "isofrequency" dimension of cortex, the highly overlapped thalamocortical connections would not, alone, predict topographic mapping of visual field elevation. Consistent with this anisotropy in thalamocortical connections that is characteristic of the auditory pathway, we find that the mapping of azimuths in the visual map is more precise than the mapping of elevations. The visual map in primary auditory cortex of lesioned ferrets thus differs from the visual map in primary visual cortex of normal ferrets (*17*), where elevations are mapped as precisely as azimuths and where the map arises from retinal input relayed through the visual thalamus to cortex along projections that are topographic along both axes of representation (Fig. 2).

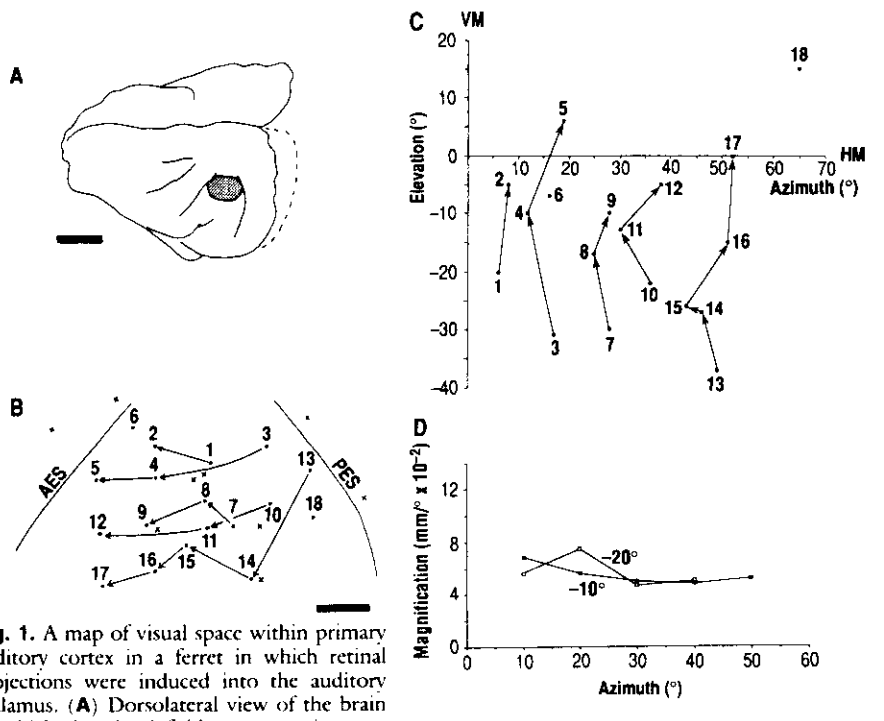

Fig. 1. A map of visual space within primary auditory cortex in a ferret in which retinal projections were induced into the auditory thalamus. (**A**) Dorsolateral view of the brain in which the visual field representation was mapped in primary auditory cortex (shown as stippled area on the brain). The dotted line represents the portion of visual cortex that was ablated at birth in this animal. Scale bar, 5 mm. (**B**) A detailed view of the recording sites within primary auditory cortex. Sites marked by an x denote penetrations in which no visual receptive field could be mapped. AES, anterior ectosylvian sulcus; PES, posterior ectosylvian sulcus. Scale bar, 1 mm. (**C**) Progressions of receptive field centers corresponding to rows of recording sites shown in (B). For clarity, the receptive fields themselves are not drawn. Receptive field diameters ranged from 4° to 20°. VM, vertical meridian; HM, horizontal meridian. (**D**) Linear magnification factors as a function of azimuthal eccentricity in the map. Factors derived along two isoelevation lines (at −10° and −20°) are shown.

At least two mechanisms may be responsible for establishment of topography in the axis of elevation of the visual map in auditory cortex. One possibility is that thalamocortical projections are more spatially restricted in the anteroposterior dimension in lesioned ferrets than in normal animals (*18*). However, retrograde labeling techniques used to study thalamocortical projections in both normal and lesioned ferrets indicate that the projections are substantially similar (*6*). A second possibility is that visual input, characterized by specific patterns of retinal activity (*19*), leads in the cortex to physiological selection of subsets of thalamic input from a potentially large set of inputs available anatomically (*20*). It has been proposed that selection of inputs occurs along the isofrequency axis in normal auditory cortex (*21*), and selection based on correlations in input activity may underlie the generation and maintenance of maps in the normal somatosensory and visual cortex as well (*22*). Regardless of mechanism, the presence of a map of visual space in auditory cortex indicates that functional topography in a cortical map is regulated significantly by the sensory receptor sheet during development.

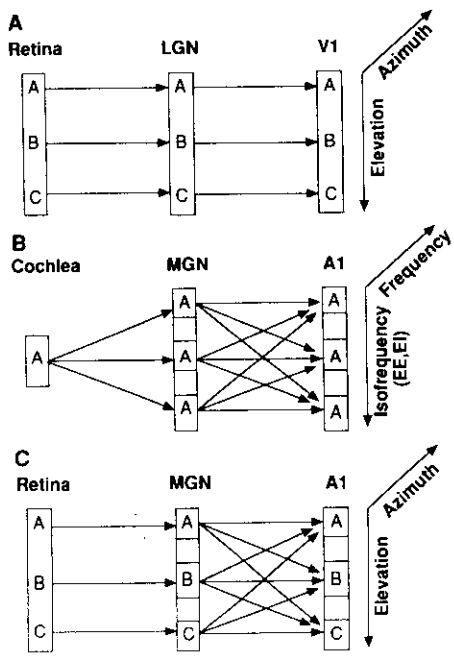

Fig. 2. Schematic representation and summary of projections from the sensory receptor surface through the thalamus to cortex in (A) the normal visual system, (B) the normal auditory system, and (C) lesioned ferrets with retinal projections induced into the auditory pathway. (**A**) In the visual pathway, each point on the retina projects in a roughly point-to-point fashion through the LGN to primary visual cortex (V1). Thus, a 2-D map of visual space exists in V1 (indicated schematically by arrows showing the mapping of visual field azimuth and of elevation along orthogonal axes on the cortex). (**B**) In the auditory pathway, each point on the cochlea projects, through intermediate relays, to a slab of cells along the isofrequency axis in the MGN. Each isofrequency slab in the MGN projects in highly overlapping fashion to its corresponding isofrequency slab in primary auditory cortex (A1). The cortex thus contains a 1-D map of the cochlea along the variable frequency axis (marked "frequency"). [Within the isofrequency axis in MGN and A1, separate clusters of neurons receive either excitation from both ears (EE neurons) or excitation from the contralateral ear and inhibition from the ipsilateral ear (EI neurons). Each EE (or EI) slab in the MGN projects to all of the EE (or EI) slabs in A1 (*15*)]. (**C**) In lesioned ferrets, we induce input from the retina, a 2-D sensory surface, into the MGN and find a 2-D visual map in A1, despite the fact that "isofrequency" slabs in the MGN still project to A1 in an overlapped way (*6*). See text for details.

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3. G. E. Schneider, *Brain Behav. Evol.* **8**, 73 (1973); D. O. Frost, *J. Comp. Neurol.* **203**, 227 (1981).
4. M. Sur *et al.*, *Science* **242**, 1437 (1988).
5. Four animals were mapped extensively and form the basis for this report. Procedures for preparing the animals for physiological recording were similar to those we have used previously (*4*). Animals were anesthetized with ketamine (30 mg of body weight per kilogram) and xylazine (2 mg/kg) and paralyzed with gallamine triethiodide (10 mg/kg per hour); their respiration was artificially controlled. Anesthesia was continuously monitored and maintained. End-tidal CO_2 was maintained at 4%. Parylene-insulated tungsten microelectrodes were used to record unit activity mostly in the middle layers of primary auditory cortex.
6. S. L. Pallas *et al.*, *J. Comp. Neurol.* **298**, 50 (1990).
7. We examined retinotopy and variability in the map in two ways. First, we plotted the azimuth of each receptive field against the mediolateral distance of the recording site from the medial edge of primary auditory cortex (and, separately, elevation against anteroposterior distance from the posterior edge of auditory cortex) and calculated a Pearson coefficient of correlation (r) along with the associated probability of departure from a random mapping. The coefficient of correlation was used because the variables under consideration, visual field azimuth (or elevation) and cortical distance, are essentially random samples from a bivariate distribution. Second, we defined a mapping index for azimuth (and separately for elevation) as the mean, over all recording sites, of |(actual value of receptive field azimuth − ideal value)|/(maximum value of azimuth represented − minimum value). We determined ideal azimuth and elevation values by overlaying isoazimuth and isoelevation lines over the mapped cortical region. The mapping index (for azimuth and elevation) would be 0 for a perfectly retinotopic map and close to 1 for a map without any topographic order.
8. For the map shown in Fig. 1, the mapping indices (±SEM) are 0.052 (±0.012) for azimuth and 0.124 (±0.055) for elevation.
9. Smoothed isoazimuth and isoelevation lines were fitted to the experimental data. Linear magnification factors, defined as the distance of cortex that represents a unit distance of visual field, were measured along a given isoelevation line as the extent of cortex representing each successive 10° of azimuth.
10. This is consistent with the demonstration that retinal W cells, which are distributed rather uniformly in the retina [D. J. Vitek, J. D. Schall, A. G. Leventhal, *J. Comp. Neurol.* **241**, 1 (1985); A. G. Leventhal, R. W. Rodieck, B. Dreher, *ibid.* **237**, 216 (1985)], provide the major input to the auditory pathway in lesioned ferrets [(*4*); A. W. Roe, P. E. Garraghty, M. Sur, *Soc. Neurosci. Abstr.* **13**, 1023 (1987); S. L. Pallas, J. Hahm, M. Sur, *ibid.* **15**, 495 (1989)]. In primary visual cortex of primates and carnivores [P. M. Daniel and D. Whitteridge, *J. Physiol. (London)* **159**, 203 (1961); R. Tusa, L. Palmer, A. Rosenquist, *J. Comp. Neurol.* **177**, 213 (1978); (*17*)], cortical magnification decreases approximately inversely with distance from central retina to the periphery, implying a logarithmic mapping of the retina on cortex.
11. Mapping indices for three other animals that were mapped extensively are (azimuth, elevation indices for each animal): 0.154 (±0.046), 0.252 (±0.079); 0.063 (±0.032), 0.278 (±0.101); 0.142 (±0.081), and 0.236 (±0.147). The correlation coefficients for the animals are (azimuth, elevation coefficient for each animal): 0.66, −0.39; 0.36, 0.35; and 0.95, 0.80. Magnification functions are very similar in different animals.
12. J. G. Kelly, P. W. Judge, D. P. Phillips, *Hear. Res.* **24**, 111 (1986).
13. Integrative properties appear to be represented along the isofrequency axis, such as discrete clusters of neurons related to EE or EI interactions between the two ears [T. J. Imig and J. Brugge, *J. Comp. Neurol.* **182**, 637 (1978); P. W. Judge and J. B. Kelly, *Soc. Neurosci. Abstr.* **14**, 651 (1988)] and the bandwidth of spectral tuning [M. L. Sutter and C. E. Schreiner, *ibid.* **15**, 1116 (1989)].
14. R. A. Andersen, P. L. Knight, M. M. Merzenich, *J. Comp. Neurol.* **194**, 663 (1980); S. Brandner and H. Redies, *J. Neurosci.* **10**, 50 (1990); (*15*). The pattern of projections from the auditory thalamus to auditory cortex in normal ferrets is very similar (*6*).
15. J. C. Middlebrooks and J. M. Zook, *J. Neurosci.* **3**, 203 (1983).
16. Our physiological mapping data (unpublished) suggest that retinal projections to the auditory thalamus are organized topographically. The projections from auditory thalamus to primary auditory cortex are as indicated in Fig. 2.
17. M. I. Law, K. R. Zahs, M. P. Stryker, *J. Comp. Neurol.* **278**, 157 (1988); A. W. Roe, S. L. Pallas, J.-O. Hahm, M. Sur, unpublished observations.
18. There are two ways by which thalamocortical projections can be widespread along the anteroposterior dimension of cortex in normal animals: (i) single thalamic cells have cortical arbors that are widespread along the anteroposterior dimension but restricted along the mediolateral dimension of cortex; and (ii) single thalamic cells have uniform cortical arbors, but cells close together have terminal fields that are widely dispersed along the anteroposterior dimension in cortex. It is possible that visual input alters either of these projection patterns in subtle ways in lesioned ferrets compared to normal ferrets.
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20. We consider input selection to occur by a change in the weights of thalamocortical or intracortical synapses [M. Sur, S. L. Pallas, A. W. Roe, *Trends Neurosci.* **13**, 227 (1990)].
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22. Evidence from reorganization of maps after lesioning portions of peripheral input suggests that maps in both somatosensory cortex [M. M. Merzenich, G. Recanzone, W. M. Jenkins, T. T. Allard, R. J. Nudo, in *Neurobiology of Neocortex*, P. Rakic and W. Singer, Eds. (Wiley, New York, 1988), pp. 41–67] and visual cortex [J. H. Kaas *et al.*, *Science* **248**, 229 (1990)] are dynamically maintained.
23. We thank P. E. Garraghty for assisting in some experiments, T. Sullivan for assistance with histology, and P. Katz for comments on the manuscript. Supported by NIH grant EY07719 and by grants from the McKnight Foundation and the March of Dimes.

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Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex

Mriganka Sur, Sarah L. Pallas and Anna W. Roe

Early developmental manipulations can induce sensory afferents of one modality to project to central targets of a different sensory modality. We and other investigators have used such cross-modal plasticity to examine the role of afferent inputs and their patterns of activity in the development of sensory neocortex. We suggest that the afferent rewiring can significantly influence the internal connectivity or microcircuitry of sensory cortex, aspects of which appear to be determined or specified relatively late in development, but that they cannot influence, or influence only to a minor extent, the laminar characteristics and external connectivity patterns of cortex, which appear to be specified earlier.

One of the most fundamental organizing principles of the cerebral cortex is the localization of function into different areas of representation. In recent years, a major goal of research into cortical mechanisms of sensory processing has been to define the functional role of different cortical areas within each modality. In the visual cortex of primates, for example, there are at least 17 and perhaps 30 or more areas, each of which contains a separate representation of the visual field and processes limited aspects of the visual scene[1–3]. While the organization of the auditory and somatosensory cortical areas is less well understood, it is clear that at least the main features of cortical organization in these modalities are similar to those of the visual system[4].

Cortical development may be thought of as a progressive restriction of the fate of cortical neurons, a process variously termed determination or specification. How are the sensory cortical areas specified during development, and how do they come to represent and process specific kinds of information? The most general answer is that cortical areas are specified intrinsically by genetically determined mechanisms, and/or that specification occurs by extrinsic factors that operate epigenetically. Several kinds of experiments have addressed this issue, and excellent reviews have appeared[5–7]; here we synthesize the results of primarily one sort of experiment that addresses the issue of cortical specification directly. These experiments involve cross-modal plasticity in development, i.e. the routing of fibers that carry information about one sensory modality into structures and central pathways that normally process a different modality.

The development of a cortical area involves the specification of several features that make up the area, including the characteristics and location of its constituent cells (cytoarchitectonics), the external connections it makes with other cortical areas and subcortical structures (i.e. its inputs and outputs), and the internal connections or microcircuitry within the cortical area. Whereas other experimental paradigms can be used to address the first of these features, the induction of cross-modal plasticity provides a paradigm that is particularly suited to addressing the role of afferents in specifying the external and internal connections of a cortical area.

Similarities and differences between sensory cortical areas

Any discussion of the specification of sensory cortex requires an understanding of which attributes

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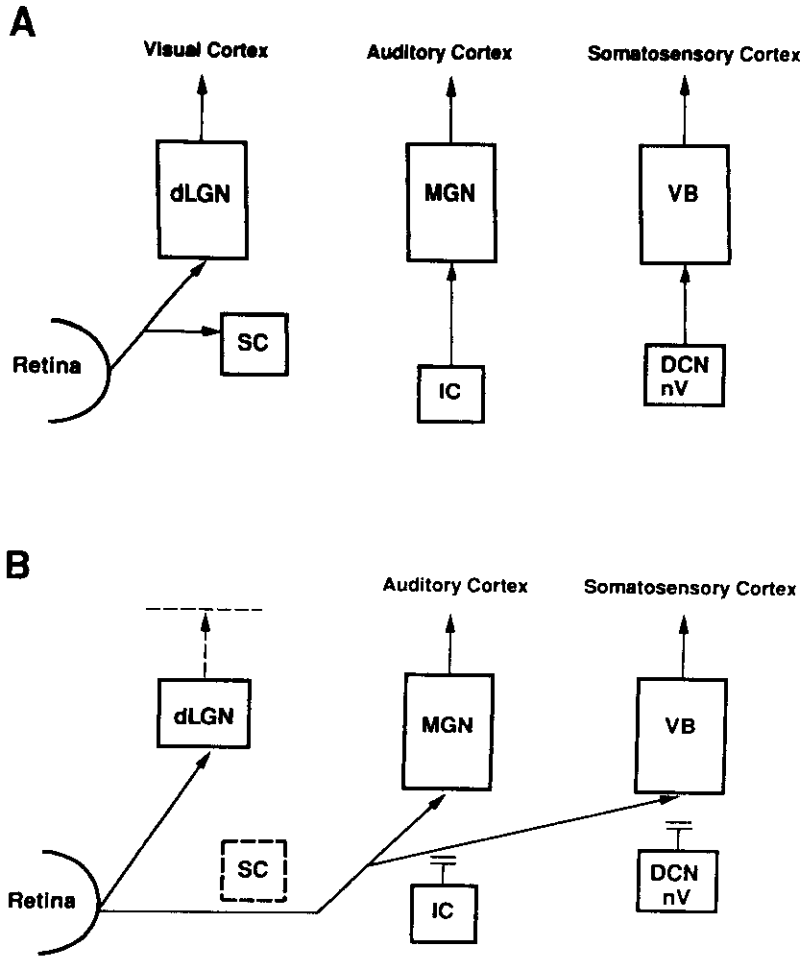

Fig. 1. *Illustration of the neonatal manipulations that lead to cross-modal plasticity of visual projections.* **(A)** *The normal connectivity pattern of the three sensory systems. The dorsal lateral geniculate nucleus (dLGN) and the superior colliculus (SC) are the major targets of the retina. In the auditory pathway, the cochlea projects, via intermediate relays, to the inferior colliculus (IC) of the midbrain, which projects to the medial geniculate nucleus (MGN). In the somatosensory pathway, the dorsal column nuclei (DCN) and the nuclei of the trigeminal nerve (nV), along with spinal afferents, project via the medial lemniscus to the ventrobasal nucleus (VB) of the thalamus.* **(B)** *This review describes the results of manipulations that route retinal projections to either the MGN in ferrets, or the VB in hamsters. On the day of birth, in either the hamster or the ferret, the SC is removed by direct ablation and the occipital cortex is ablated, causing the dLGN to degenerate. MGN or VB is deafferented by sectioning the major input pathways. The retina then invades the deafferented thalamic nucleus, which retains its normal cortical termination site. Visual responses can thus be elicited from cells in auditory cortex (AI) or somatosensory cortex (SI/SII).* (Modified from Refs 40, 44.)

are unique to each sensory cortical area in the adult brain, and which are common to all. Cortical areas were originally subdivided on the basis of cytoarchitecture[8], which is quite distinct between the different areas. Factors that contribute to these cytoarchitectonic differences include the type, number, size and arrangement of constituent neurons, and the arrangement of myelinated fibers among the cortical layers. Also, areas can differ in their corticocortical and subcortical connectivity patterns, in their topography, in the response properties of their neurons, and in their behavioral role.

At the same time, there are many underlying similarities between different cortical areas. The number of anatomical similarities is striking. All areas of neocortex are composed of six layers of cells, each of which contains characteristic cell types. Primary sensory cortices are often referred to as 'granular', reflecting the prominence of the small-celled layer IV. A common organizational principle is the modular organization of afferents and cortical processing circuitry of similar functional types[9]. In addition, there are gross similarities in the pattern of interlaminar connections, and in the laminar origin of extrinsic connections[10–12]. Widespread horizontal connections, appreciated relatively recently in area 17 (Refs 13, 14), may also be a feature common to most or all areas of sensory neocortex (see, for example, Ref. 15).

Apart from these anatomical similarities, there may be significant similarities in functional aspects of neurons in different areas, even between areas that represent different modalities. Neurons selective for both the velocity and direction of the stimulus are found in auditory, visual and somatosensory cortex[16–18]. Topographic maps and some form of contrast enhancement, or lateral inhibition, also seem to be universal features of sensory pathways, including those in cortex.

Thus, sensory neocortex appears to consist of a basic structure held in common by all cortical areas, on which is superimposed a number of area-specific differences. A reasonable hypothesis is that similar aspects are intrinsically determined, perhaps before interaction with extrinsic influences (via afferent input) has occurred. Conversely, differences between areas may arise from extrinsic or afferent-induced factors, presumably at a later stage of development. This would apply not only to cortical areas of different modalities, but also to areas processing different subsets of inputs within a given modality (e.g. color, form, or motion in the visual pathway). This hypothesis provides a framework for identifying intrinsic and extrinsic components for each of the features that defines the identity of an area.

Cortical differentiation and specification include at least three different processes; radial specification (the development of the laminar pattern typical of each cortical area), development of external connections (with subcortical or other cortical structures), and development of internal circuitry (i.e. the local connections, or microcircuitry within and between cortical columns). We review briefly the evidence for afferent control of each of these processes.

Radial specification of cortex

The radial development of the cortex begins with proliferation of precursor cells at the ventricular layer[6,19]. These cells then migrate out along radial glial fibers in an inside out manner; the earliest born cells reside deepest in the cortex and vice versa. Thus, the birthdate of a cortical neuron is a powerful predictor of its final laminar position. McConnell[5,20,21] has evidence from heterochronic transplants that many cells are committed early to their laminar fate.

The laminar distribution of cortical cells may also be influenced by thalamic inputs. This idea is supported by the positive correlation between the thickness of layer IV in different cortical areas and the amount of thalamic afference each area receives (see Refs 22, 23 for review). Thalamic afferents wait underneath the

cortical plate as the presumptive layer IV cortical cells migrate through them on their way to their laminar destination[24,25]. This waiting period may provide an opportunity for interaction between the afferents and their cortical target cells. Ablation of large regions of the thalamus prior to migration of layer IV neurons drastically reduces the number of neurons in layer IV (Ref. 26). However, tritiated thymidine labelling suggests that some of the cells originally destined for layer IV can be respecified into layer II–III cells in the absence of their thalamic input.

Development of external connectivity patterns

Each cortical area has a unique pattern of input and output connections. However, early in development, single cortical cells send collaterals to many targets that they later retract. Thus, motor cortex and visual cortex both project to the pyramidal tract in neonatal rats, but visual cortical cells withdraw these projections[7]. Similarly, callosal projections are initially widespread and are restricted later by collateral elimination (see Ref. 7 for review).

There is increasing evidence that at least the basic afferent and efferent connections of a cortical area are established early in development. Shatz and colleagues have shown that a population of cells in the cortical subplate, which appears before the generation of the six cortical layers, projects toward subcortical and callosal target areas at very early developmental stages[27,28]. These subplate cells largely disappear by adulthood, but the efferent projections of subplate neurons may form early guides for later corticofugal (and thalamocortical) axons[29]. In principle, at least, the subplate cell axons may pioneer the early, exuberant projections to and from cortical areas as well as the restricted projections found in the adult.

The final connectivity pattern of cortical cells is not rigidly predetermined, however, and can be influenced by outside factors. O'Leary and Stanfield[30] have reported that the development of specific cortical efferent projections can be influenced by location. They transplanted pieces of late fetal (E17) rat neocortex from visual cortex to sensorimotor cortex or vice versa, and found that the donor tissue makes final projections appropriate to the host tissue. These results suggest that some property of the surrounding host cortical tissue (such as its inputs or its location) may influence the connectivity of the donor tissue independent of its origin.

Development of internal cortical microcircuitry

At present, little is known about the role of afferents in the development of the microcircuitry responsible for the response characteristics of cortical cells. Afferents and their activity patterns clearly play an important role in the development of neuronal response properties in the cortex, and there is an extensive literature on the effects of altering activity or experience on the responses of sensory cortical neurons[31,32]. However, in the experiments we discuss below, the modality (and hence the activation pattern) of the afferents innervating a cortical area is changed without changing the thalamocortical identity of these afferents. Such experiments provide an alternative way to address the issue of afferent control of intrinsic connectivity.

Cross-modal studies: rerouting of sensory projections

In 1973, Gerald Schneider first described a series of experiments in the hamster[33] that was to open the way for a direct investigation of the role of afferent inputs in specifying cortical processing circuitry. Schneider noted that retinal axons could sprout into nearby deafferented areas if the normal retinal targets were removed by neonatal brain lesions. For example, lesions of the superior colliculus (SC) that extended into the inferior colliculus (IC), which provides the major afferent input to the auditory thalamus, resulted in abnormal retinal projections into the auditory relay nucleus of the thalamus, the medial geniculate nucleus (MGN) (Fig. 1). Kalil and Schneider[34] obtained ultrastructural evidence demonstrating that these retinal axons make synaptic connections in the MGN.

Since these pioneering studies, cross-modal rewiring has been demonstrated in a number of different preparations. Devor[35] showed that hamster olfactory afferents can regenerate after section of the lateral olfactory tract in neonates, but that they regenerate into inappropriate cortical regions. Graziadei *et al.*[36]

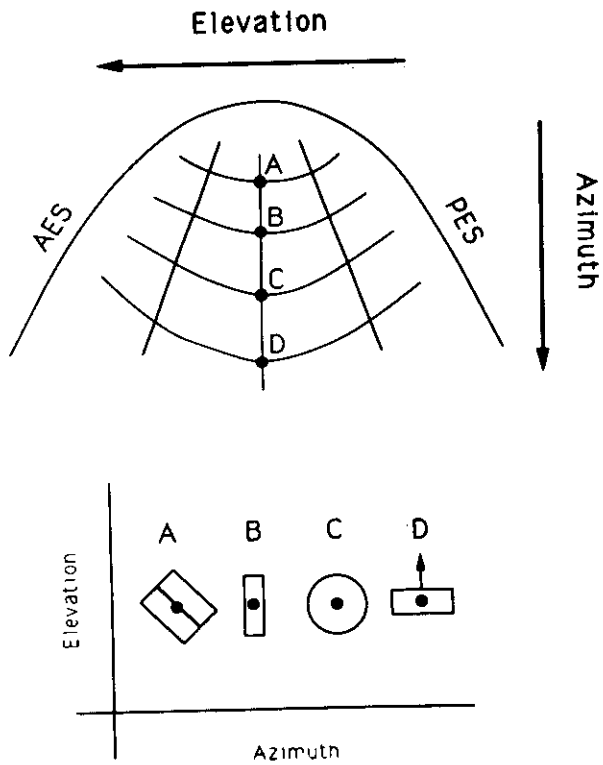

Fig. 2. *Results of physiological recordings of visually responsive cells in AI of rewired ferrets. A two-dimensional visuotopic map is created in AI as a result of retinal input to the auditory pathway. Elevations of visual receptive fields recorded in AI increase in a posterior–anterior direction, and azimuths increase in a mediolateral direction on the cortical surface. As shown schematically, visual units recorded at points along a line of constant elevation from A to D in AI have receptive field locations that increase in visual field azimuth (A–D, bottom). The bottom schematic also illustrates physiological characteristics of visual units in AI. Receptive field types recorded in AI can be rectangular, with orientation and direction selectivity (indicated by an arrow on one field), and with or without subfields; many receptive fields are circular.*

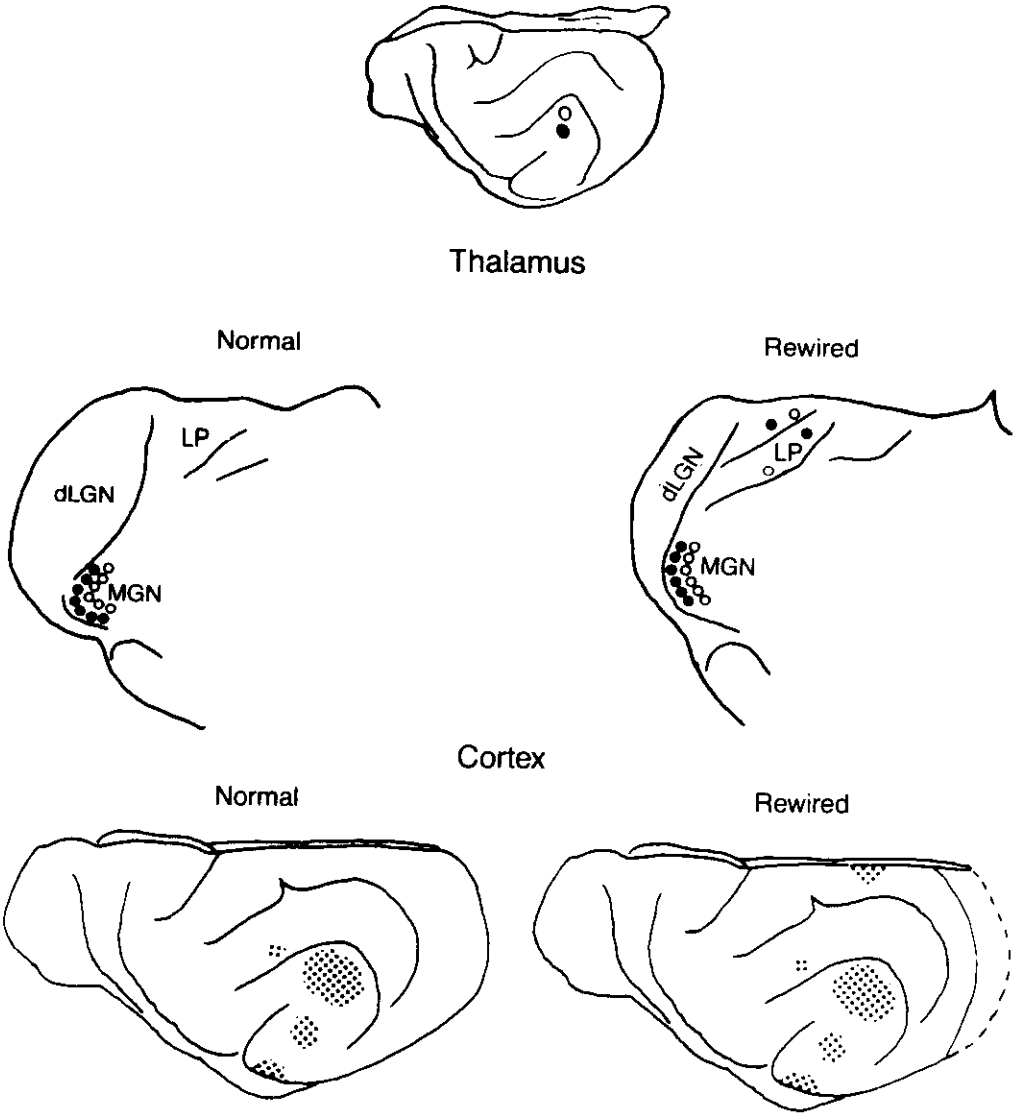

Fig. 3. *Patterns of thalamocortical and corticocortical connections in normal and rewired ferrets.* Thalamus: *following injections of neuroanatomical tracers in AI (which lies lateral to the suprasylvian sulcus, as indicated by the dotted line), labeled cells are seen in the medial geniculate nucleus (MGN) in both normal and rewired animals. In the latter, there are a few additional labeled cells in the dorsal thalamus, particularly in the region of the lateral posterior nucleus (LP). As shown by injections of two different dyes at topographically separate locations in AI, the one-dimensional pattern of the MGN-to-AI projection is unchanged by the early lesions. See text for details.* Cortex: *cortical inputs (and outputs) of AI, shown as hatched areas along with AI, are similar in normal and operated animals (with the exception of a projection from medial cortex in rewired animals that is sparse in normal animals). Other abbreviations: dLGN, dorsal lateral geniculate nucleus.*

demonstrated that olfactory afferents regenerate following unilateral olfactory bulbectomy in neonatal mice, and that these regenerating axons can innervate neocortex rather than their normal olfactory bulb target.

Studies in mole rats *(Spalax ehrenbergi)* have taken advantage of a natural evolutionary diversion of auditory afferents into visual structures[37]. Mole rats have only vestigial eyes, and their retinal axons largely degenerate during development. As a result, the LGN and occipital cortex receive auditory input[38,39], and response properties typical of auditory cortex are recorded in occipital cortex (Heil, P. and Scheich, H., pers. commun.).

Frost has shown that the hamster retina can also be induced to project to the ventrobasal nucleus (VB), the principal somatosensory relay nucleus of the thalamus, again by reduction or removal of normal retinal targets and transection of ascending afferent inputs to VB[40]. Unlike the retinal projection to MGN, the retinal projection to VB results in part from the stabilization of an early, exuberant projection[41].

These studies indicate that, while there may be a preference of sensory axons for their normal termination sites, they will innervate other sensory areas either within or across sensory modalities if their normal target is not available.

Visual projections induced into primary somatosensory and primary auditory cortex

Studies of cross-modal plasticity can provide information about the afferent control of cortical specification, and they can reveal inherent differences or similarities between different sensory neocortical areas. What effect, if any, does changing the modality of the information carried by the thalamic afferents have on cortical processing? Can somatosensory and auditory cortex make use of visual information, and if so, do they perform transformations on that input that are typical of normal visual cortex?

In our laboratory, we have generalized the paradigm in Schneider's early work to another mammal, the ferret *Mustela putorius furo*. Ferrets have a number of advantages for this type of study. Like hamsters, they are born in an immature state, facilitating manipulations of the developing nervous system. The organization of their visual pathway closely resembles that in cats; the ferret retina contains X and Y retinal ganglion cells, as well as a third, heterogeneous group of cells collectively termed W cells[42–44]. In ferrets, retinal afferents can be induced to project into the MGN by reducing the normal retinal targets and by providing alternative target space in the MGN (Fig. 2). We have demonstrated that retinal W cells are responsible for the aberrant projection in rewired ferrets[44].

Response characteristics of visual neurons

Our electrophysiological studies show that visually responsive cells can be recorded in the MGN of rewired ferrets. Since the pathway from MGN to auditory cortex has not been disrupted but carries visual information as a result of the lesion, cells in primary auditory cortex (AI) also respond to visual stimulation. Visual cells in AI have large receptive

fields. About one-third of the fields are orientation-selective, and a similar proportion are direction-selective[44] (Roe, A. W., Pallas, S. L. and Sur, M., unpublished observations). The oriented receptive fields have either separate or co-extensive ON and OFF zones and hence resemble receptive fields of simple or complex cells in normal visual cortex[45] (Fig. 2, bottom). A number of cells are driven binocularly.

Results from hamsters with retinal projections to somatosensory thalamus also show that responses typical of visual cortex can be elicited from non-visual cortex. Metin and Frost[46] found that neurons in somatosensory cortex (area SI/SII) have responses to visual stimuli similar to those of cells in area 17 of normal animals. As in area 17, the cells in SI/SII respond to flashing spots or bars, and their receptive fields are often organized into concentric or adjacent subfields of ON, OFF, or ON/OFF types. The percentage of cells showing orientation and direction selectivity is similar to that found in area 17.

Anatomical organization of cortical projections

Does the rewiring procedure affect the external connections of AI, and might there be other pathways for visual input to AI? To answer these questions, we have made injections of anterograde and retrograde tracers into AI in rewired ferrets. These studies reveal that, in addition to the connections with MGN and the posterior thalamic group that resemble those in normal animals, AI in the rewired ferrets makes anomalous, reciprocal connections with the dorsal thalamic area, including the lateral posterior nucleus of the thalamus (LP)[47] (Fig. 3). While there are also anomalous projections from the retina to LP in these animals, these new projections are quite sparse, and we think they are unlikely to have a major influence on visual processing in AI. Corticocortical connections of AI are similar in normal and rewired animals.

We have also examined the details of the thalamocortical projection from the MGN to AI in the rewired ferrets. In normal ferrets[47], as in cats[48,49], focal injections of retrograde tracers into AI label laminae or slabs of cells that are oriented dorsoventrally within the MGN and extend as sheets of projection in the rostrocaudal dimension of the nucleus. We interpret these slabs to correspond to physiologically defined isofrequency slabs in the MGN[49]. Consistent with this idea, injections of multiple tracers along the tonotopic axis in AI label non-overlapping slabs in the MGN, while injections along the isofrequency axis label overlapping slabs[47]. This pattern of essentially one-dimensional projections in the auditory pathway is fundamentally different from the pattern of two-dimensional projections that characterizes the retinogeniculocortical pathway, and the pattern remains unchanged in the rewired ferrets (Fig. 3).

Topography of visual representation

The primary auditory cortex in normal ferrets, as in other animals, contains a one-dimensional, cochleotopic map of sound frequency[50,51]. Visual input to AI results in a two-dimensional visual field map with elevation increasing from caudal to rostral, and azimuth increasing from medial to lateral[52] (Fig. 2, top). The azimuthal axis, which corresponds to the tonotopic axis in normal animals, contains an orderly progression of visual field location. The elevational

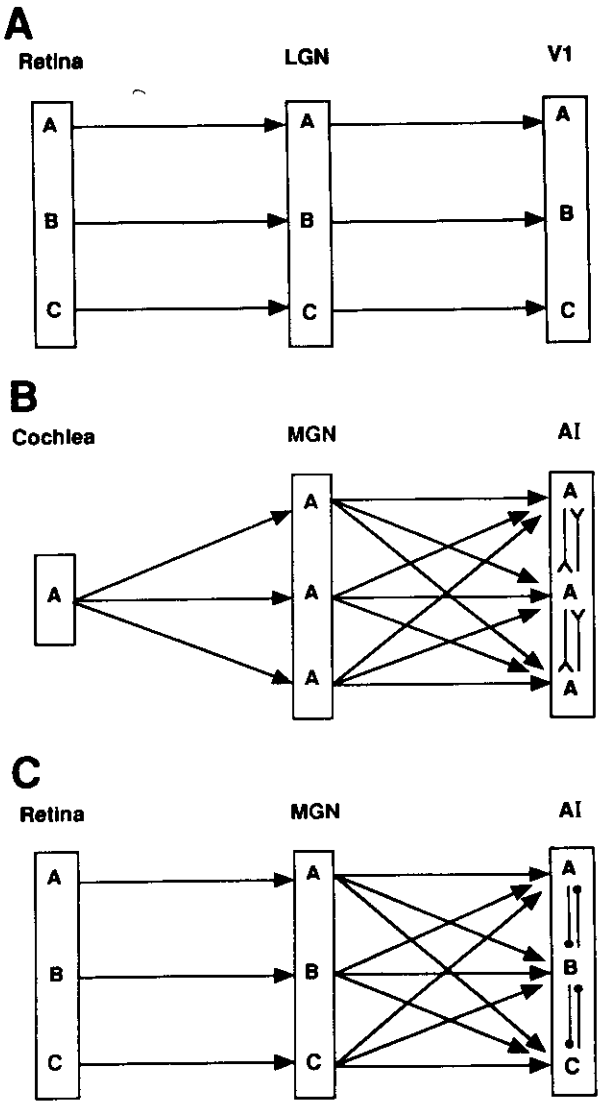

Fig. 4. *Highly schematic representation and summary of thalamocortical projections in (A) the normal visual system, (B) the normal auditory system, and (C) the retina-to-MGN-to-AI projection in rewired ferrets.* **(A)** *Each point on the retina projects in a roughly point-to-point fashion through the lateral geniculate nucleus (LGN) onto visual cortex (V1), and each neuron in V1 'sees' a limited region of visual space.* **(B)** *In the auditory system, the cochlea contains a one-dimensional representation of sound frequency, and each point on the cochlea is represented in a redundant fashion along a slab of cells in the MGN[49]. Isofrequency slabs in MGN are thought to project in a highly overlapped fashion to AI, such that any neuron in AI receives input from a large number of neurons along the MGN slab representing the same frequency[48,49].* **(C)** *In the rewired ferrets, we impose a two-dimensional input from the retina onto the MGN. The nature of the retina-to-MGN projection has not yet been examined in detail (but see Ref. 44), so this part of the schematic is hypothetical. Because the MGN still projects in a highly convergent and divergent fashion to AI (Ref. 47), we hypothesize here that the spatially restricted visual fields and the visual field map in AI arise from changes in the intrinsic circuitry of AI. We have schematized one possible scenario for this change by postulating changes in lateral connections along the isofrequency dimension in AI (which lies anteroposteriorly in cortex). Lateral inhibitory connections between neighboring locations in AI would have the effect of silencing a subset of the thalamic inputs, creating spatially limited receptive fields.*

map, along the normal isofrequency axis, is less precise, and the maps can vary in polarity between animals. We suggest that the mapping along this dimension is created in cortex, perhaps by dynamic alterations in intrinsic connectivity during development (see below).

Somatosensory cortex in hamsters, as in other mammals, normally contains a two-dimensional map of the body surface that is transmitted from VB. However, in rewired hamsters, there is a systematic progression of visual receptive fields only from superior to inferior retina, and therefore essentially a one-dimensional visual field map in SI/SII (Ref. 53). The nasotemporal axis of the retina is apparently collapsed onto the isorepresentational axis in VB, and thus the second dimension is 'lost' in cortex.

Role of afferents in cortical specification

What do these studies of cross-modal plasticity suggest about the influence of thalamocortical afferents and their patterns of activity on the development of sensory cortex? The receptive field properties of visually responsive cells in SI/SII in hamsters and in AI of ferrets demonstrate that at least some of the transformations in stimulus representation that occur in normal visual cortex can also occur in AI or SI/SII if they receive visual input.

It is possible that there are some basic processing modules in all sensory cortices that perform stereotypical transformations on their inputs regardless of modality. Thus, visual inputs to SI/SII or to AI simply tap into these modules. The idea of similar cortical processing modules is supported by commonalities in processing between different primary sensory cortices. In the somatosensory cortex, there are straightforward parallels to two of the basic transformations that striate cortex performs on its visual inputs: direction selectivity and orientation selectivity have both been described for neurons in postcentral somatosensory cortex[17,18]. In AI, neurons that respond to the direction and rate of modulation of sound frequency have been described[16,54]. It is possible that processing modules in AI that respond to complex notes or chords[55], and hence to simultaneous stimulation of discrete regions of the sensory epithelium, would generate patterns of orientation selectivity when they receive visual input. Still, given the one-dimensional nature of the cochlea and of sound transduction, generalizing such modules to generate orientation selectivity in auditory cortex for two-dimensional visual stimuli is not straightforward. There are also significant differences between different areas of visual and somatosensory cortex in the types and proportions of neurons with various response properties[32,56]. Thus, while there may be a basic framework of similar modules in neocortical organization and development, afferents must also play a significant role in regulating intrinsic cortical microcircuitry.

We suggest that, in auditory cortex of rewired animals, those physiological features that depend on the two-dimensional nature of visual input arise as a result of alterations in the intrinsic microcircuitry of AI. The anatomy of thalamocortical projections between MGN and AI in normal and rewired animals (Fig. 3) would predict that visual fields of neurons in AI would be anisotropic (i.e. elongated along one dimension), since single neurons in AI would receive inputs from a slab of cells in MGN (and presumably from an elongated strip of retina). However, single neurons in AI of the rewired ferrets have spatially restricted receptive fields, and AI contains a systematic two-dimensional map of visual space. One possible interpretation consistent with our anatomical and physiological observations is that local inhibition in AI, driven by correlated activity patterns between neighboring elements in the retina, physiologically sharpens the receptive fields of single neurons (Fig. 4) and thus generates the overall visuotopic map as well. Retinal activity, and hence retinal afferents, might play an instructive role in shaping intrinsic cortical connectivity, particularly those intrinsic connections that occur along the isofrequency dimension in AI (Ref. 15). It is important to emphasize that changes in internal connections or microcircuitry need not imply gross changes in intracortical connections, and may include changes in the weights of pre-existing synapses or in the balance of excitation and inhibition on cortical cells. In principle, it is also possible that retinal afferents to auditory thalamus alter the pattern of thalamocortical projections in subtle ways, directing the visual field map in AI. Addressing these issues requires more detailed anatomical and physiological experiments, and this is an important goal of our work at present.

Temporal determinants of cross-modal plasticity

Why do the early lesions in ferrets (and the consequent switch of input modality) produce changes in response properties and topography in AI so that it functionally resembles visual cortex, but no change in corticocortical connectivity and only minor changes in the thalamocortical connectivity of AI (Refs 44, 47)? One possible reason is that the external connectivity patterns of AI and visual cortex are inherently different and cannot be influenced by experimental manipulation. Alternatively, it is possible that the lesions were made too late for afferents to have an influence.

These possibilities can be examined by looking at the time course of cortical development in ferrets. On the day of birth, when the lesions to induce rewiring are made, the infragranular layers of cortex are migrating into position[57], and thalamocortical afferents have not quite reached the cortical plate[58]. Thus, thalamocortical and intrinsic connectivity patterns have not yet been established at birth. However, the cortical efferent pathways may already have been laid down by the subplate pioneers[29], and the laminar arrangement of cortex has been largely specified[5]. Our results then support a role for temporal factors in the lesion-induced effects: major changes could be induced only in those aspects of cortical development that were not already specified at the time of the lesions. The minor changes that were seen in extrinsic connectivity may be due to differential time courses for different thalamocortical projections (such as those from the lateral posterior nucleus of the thalamus).

Temporal factors are also important in retinothalamic connectivity. Projections of the retina become more stabilized and less plastic with age[59], suggesting a critical period for the induction of cross-modal

plasticity. After postnatal day 3 in the normal hamster, the transient retino-VB projections are eliminated[40], thus removing the substrate for inducing retinal projections to the somatosensory pathway. In ferrets, the small (presumably W) cells that arise last in the retina[60] may be the cells that project to the MGN following neonatal lesions, and earlier manipulations may allow retinal X and Y cells to project to the auditory pathways as well.

Concluding remarks

The specification of sensory cortex involves a progressive restriction of fate[5], or a sequential determination from 'protocortex'[7] to maturity. While these events are overlapped in time, laminar identity is apparently determined early, callosal and efferent connections next, then thalamocortical connections, and finally, the intracortical circuitry responsible for the physiological properties of neurons. Apart from intrinsic or genetic determinants, each specification event probably has a critical period when epigenetic factors may influence its outcome. Manipulations of the organism during development will thus have different results depending on how far the restriction of fate has progressed at the time of manipulation. Experiments on cross-modal plasticity suggest basic commonalities in cortical processing modules as well as a role for afferents in specifying intrinsic microcircuitry. These experiments have thus provided important new insights into the control of later stages of cortical development. In the future, earlier manipulations may allow us to address how the specification of early stages occurs as well.

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