INTERNATIONAL ATOMIC ENERGY AGENCY
UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION
INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
I.C.T.P., P.O. BOX 586, 34100 TRIESTE, ITALY, CABLE: CENTRATOM TRIESTE

H4.SMR/473-17

COLLEGE ON NEUROPHYSICS

"Neural correlates of behaviour, development, plasticity and memory"

1-19 October 1990

Experimentally induced visual projections into auditory thalamus and cortex

Mriganka Sur* Preston E. Garraghty and Anna W. Roe
Massachusetts Institute of Technology
Cambridge, MA USA

Reprint Series
9 December 1988, Volume 242, pp. 1437–1441

SCIENCE

Experimentally Induced Visual Projections into Auditory Thalamus and Cortex

MRIGANKA SUR,* PRESTON E. GARRAGHTY, AND ANNA W. ROE

Experimentally Induced Visual Projections into Auditory Thalamus and Cortex

MRIGANKA SUR,* PRESTON E. GARRAGHTY, ANNA W. ROE

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*).

Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139.

*To whom correspondence should be addressed.

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

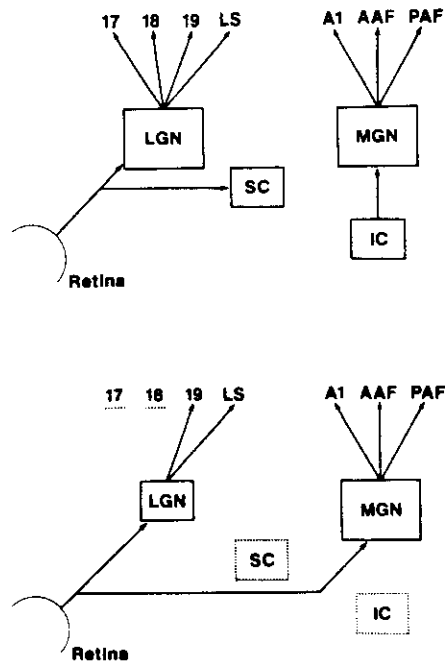

Fig. 1. The experimental design for induction of visual projections to the auditory system in ferrets. (**Top**) Projections in normal animals. The retina projects to LGN and superior colliculus (SC). The LGN projects to cortical areas 17 (primary visual cortex or striate cortex) and 18 as well as to 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

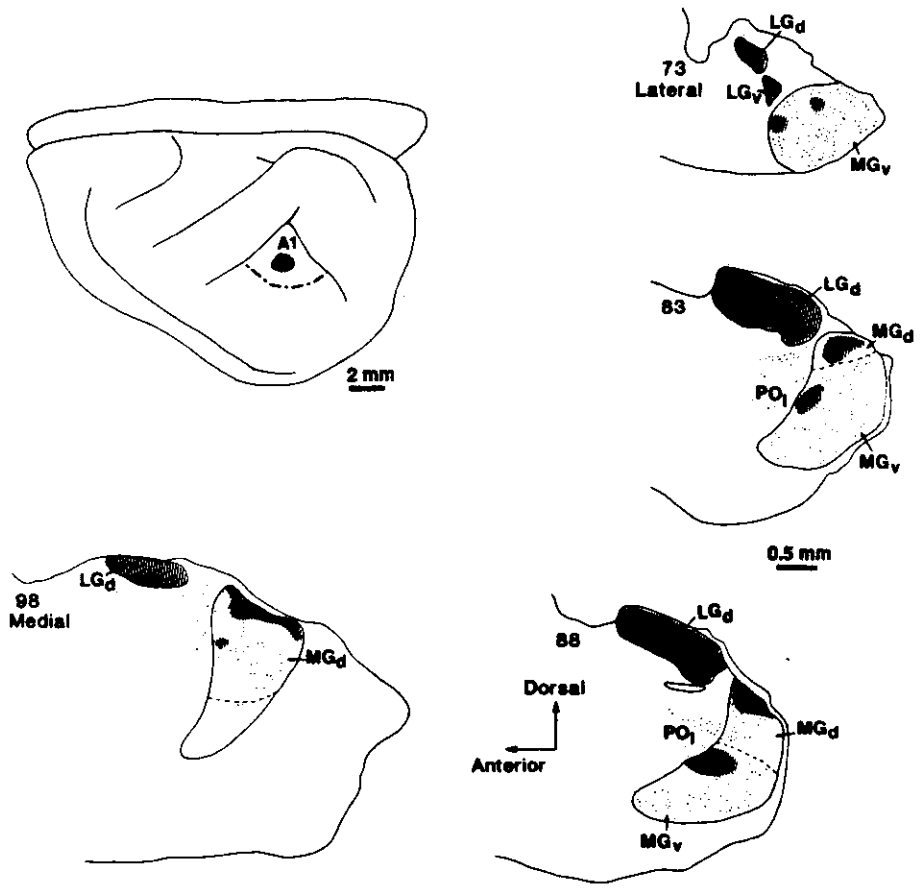

Fig. 2. Experimentally induced retinal projections (hatched areas) to the auditory thalamus and the connections of auditory thalamus with auditory cortex. The eye contralateral to the operated hemisphere projects to the surviving dorsal LGN (LG_d) and ventral LGN (LG_v) as well as to patches within the 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-

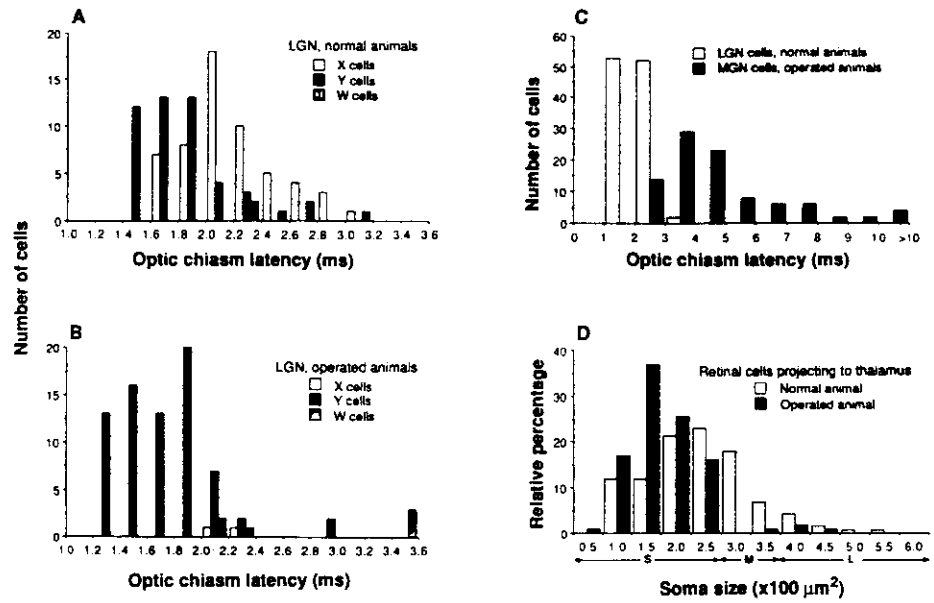

Fig. 3. Electrophysiological results from the thalamus of operated and normal animals and anatomical labeling of retinal ganglion cells that provide input to the thalamus in these animals. (**A**) The distribution of the latencies of firing, after electrical stimulation of the optic chiasm, of X, Y, 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.

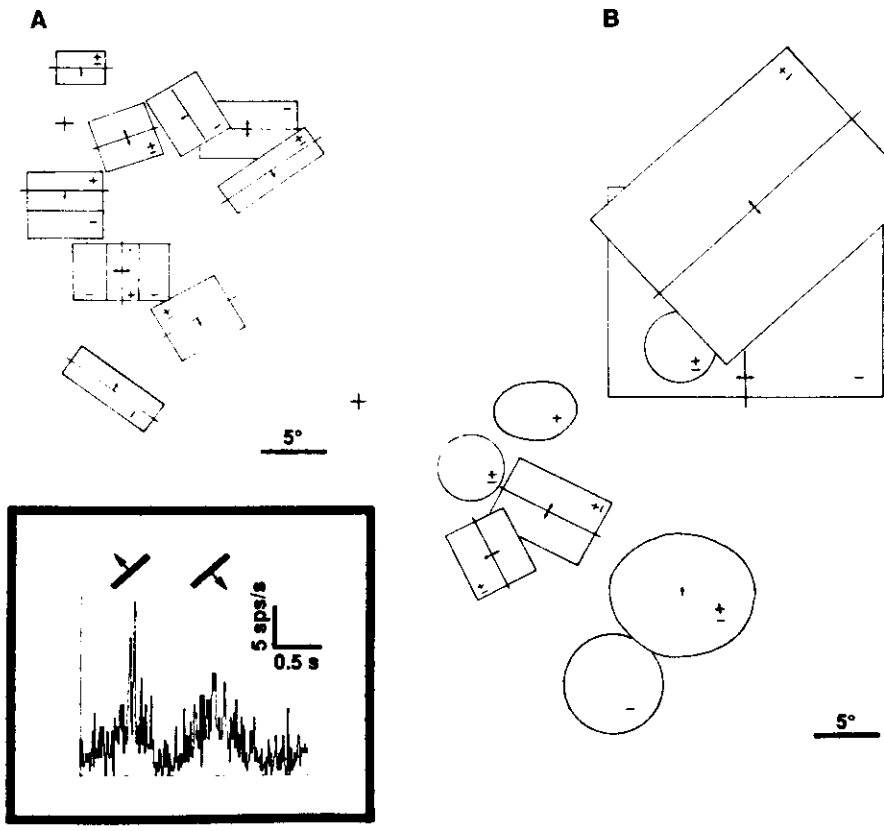

Fig. 4. Receptive fields of visual cells in primary auditory cortex of an operated animal with visual projections induced into the auditory system and comparison with receptive fields in primary visual cortex of a normal animal. Cells were classified as nonoriented or oriented simple or complex according 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).
12. M. A. McCall *et al.*, *ibid.*, p. 591.
13. L. Tong *et al.*, *Science* **217**, 72 (1982).
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.

29. L. M. Aitkin, D. R. F. Irvine, W. R. Webster, in *Handbook of Physiology: The Nervous System*, I. Darian-Smith, Ed. (American Physiological Society, Bethesda, MD, 1984), vol. 3, pp. 675–737.
30. M. I. Law and M. P. Stryker, *Invest. Ophthalmol. Visual Sci. Suppl.* **24**, 227 (1985).

31. We thank A. Graybiel, P. Schiller, and G. Schneider for comments on the manuscript, D. Frost and P. Rakic for help and advice, and M. MacAvoy and T. Sullivan for technical assistance. Supported by NIH grants EY07023 and EY07719, March of Dimes grant 1-1083, and the McKnight Foundation.

4 August 1988; accepted 27 September 1988

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

Correspondence should be addressed to Mriganka Sur.

Mriganka Sur, Sarah L. Pallas and Anna W. Roe are at the Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

  0166 - 2236/90/$02.00

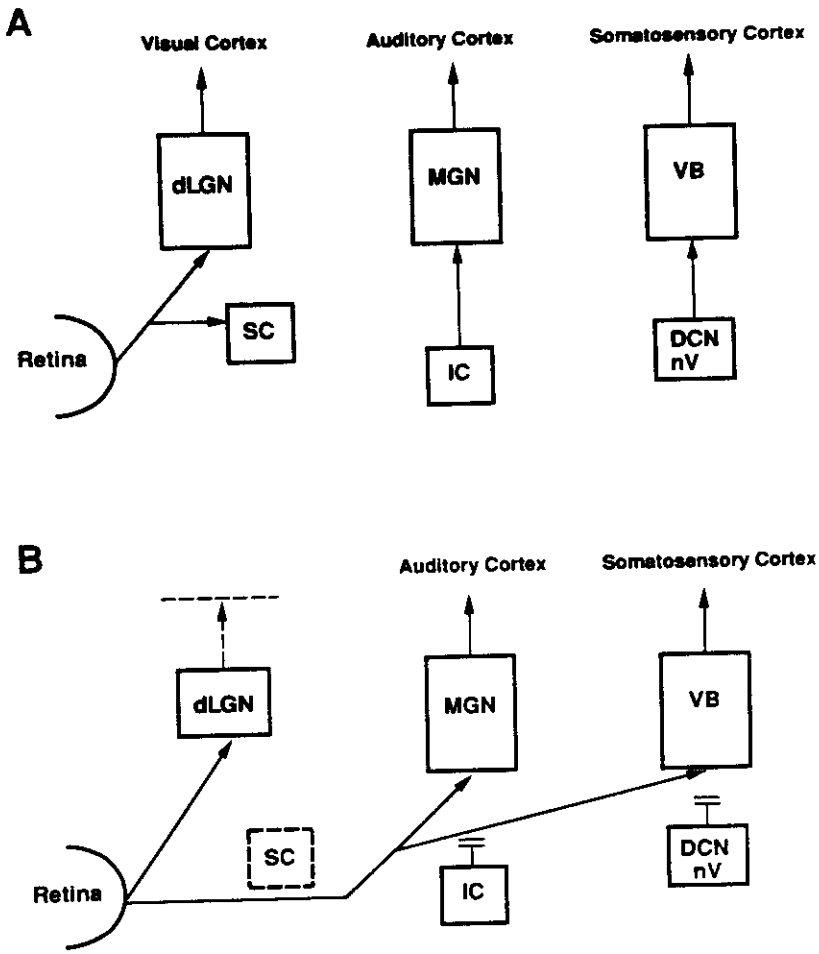

Fig. 1. *Illustration of the neonatal manipulations that lead to cross-modal plasticity of visual projections.* **(A)** *The normal connectivity pattern of the three sensory systems. The dorsal lateral geniculate nucleus (dLGN) and the superior colliculus (SC) are the major targets of the retina. In 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]

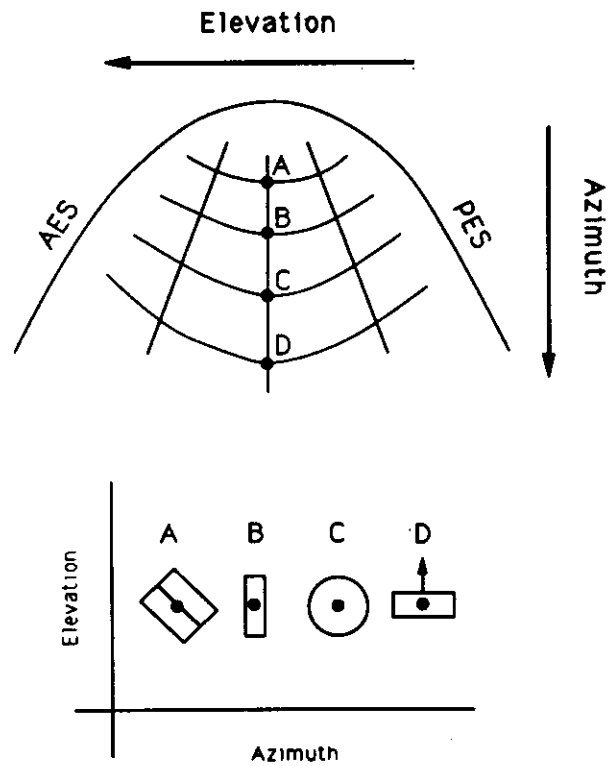

Fig. 2. *Results of physiological recordings of visually responsive cells in AI of rewired ferrets. A two-dimensional visuotopic map is created in AI as a result of retinal input to the auditory pathway. Elevations of visual receptive fields recorded in AI increase in a posterior–anterior direction, 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.*

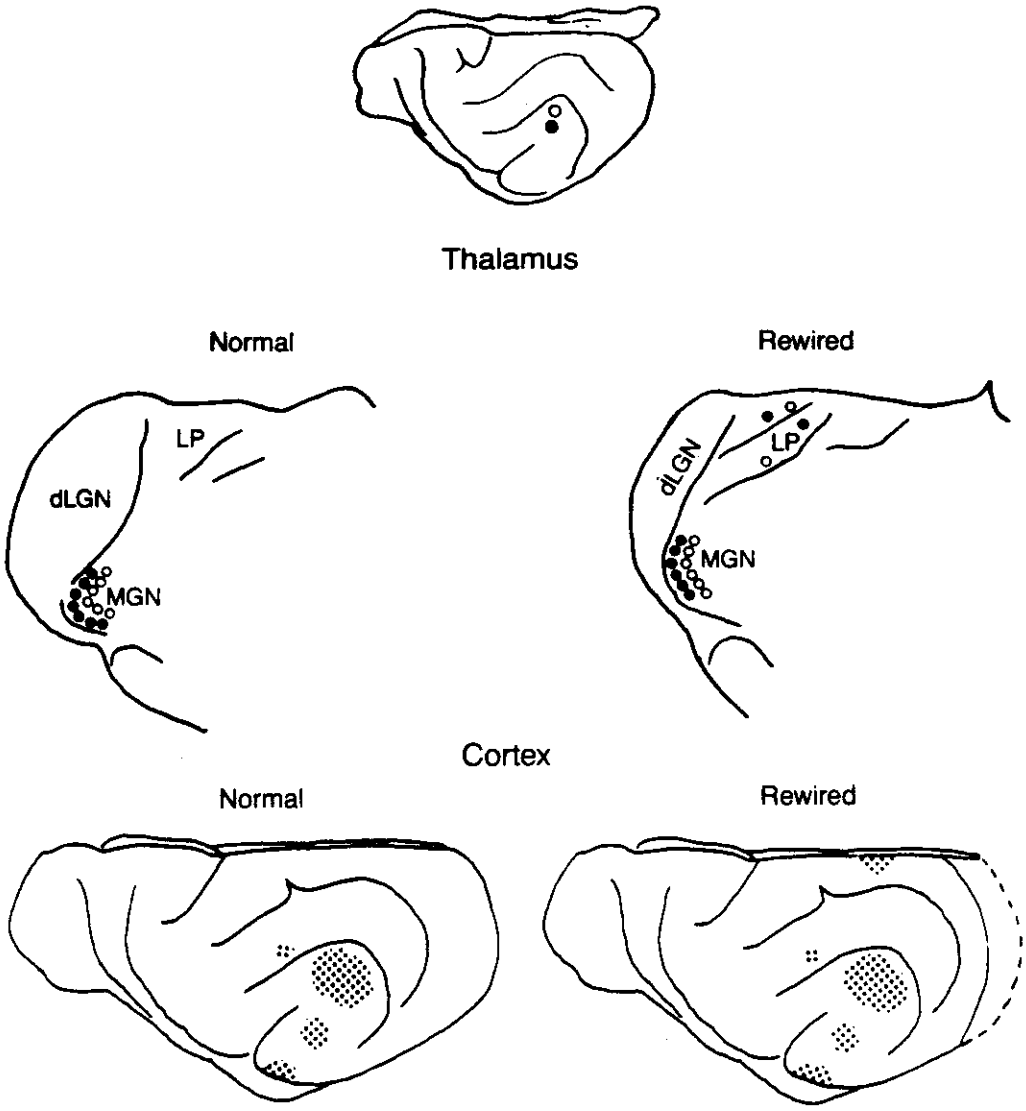

Fig. 3. *Patterns of thalamocortical and corticocortical connections in normal and rewired ferrets.* Thalamus: *following injections of neuroanatomical tracers in AI (which lies lateral to the suprasylvian sulcus, as indicated by the dotted line), labeled cells are seen in the medial geniculate nucleus (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

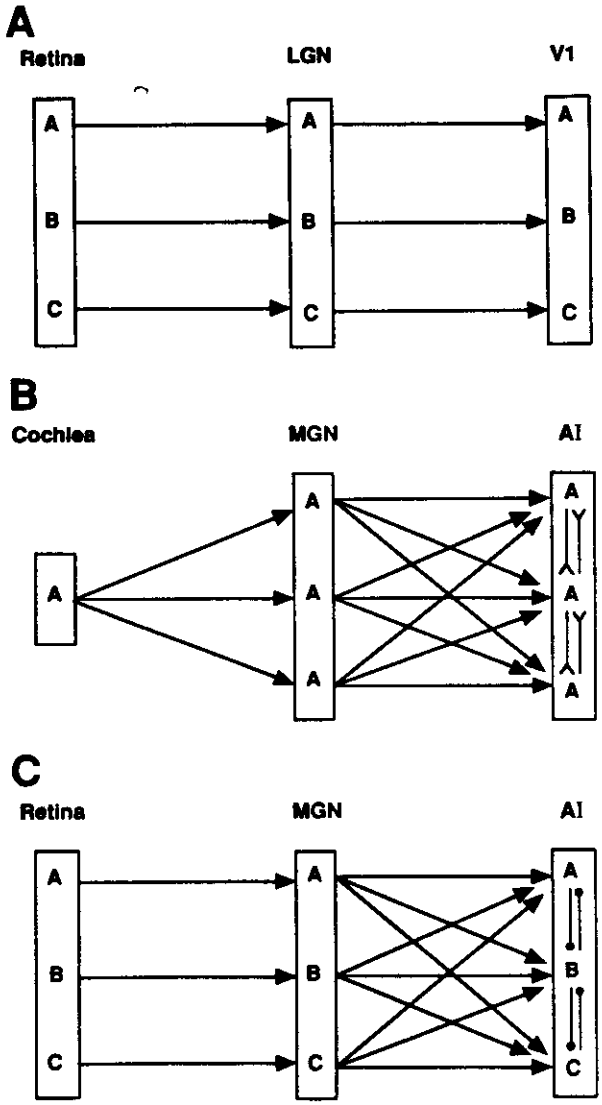

Fig. 4. *Highly schematic representation and summary of thalamocortical projections in (A) the normal visual system, (B) the normal auditory system, and (C) the retina-to-MGN-to-AI projection in rewired ferrets.* **(A)** *Each point on the retina projects in a roughly point-to-point fashion through the 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.

Selected references

1 Van Essen, D. C. (1985) in *Cerebral Cortex, Vol. 3: Visual Cortex* (Peters, A. and Jones, E. G., eds), pp. 259–330, Plenum Press
2 Livingstone, M. S. and Hubel, D. H. (1988) *Science* 240, 740–749
3 Maunsell, J. H. R. and Newsome, W. T. (1987) *Annu. Rev. Neurosci.* 10, 363–401
4 Merzenich, M. M. and Kaas, J. H. (1980) *Prog. Psychobiol. Physiol. Psychol.* 9, 1–42
5 McConnell, S. K. (1989) *Trends Neurosci.* 12, 342–349
6 Rakic, P. (1988) *Science* 241, 170–176
7 O'Leary, D. D. M. (1989) *Trends Neurosci.* 12, 400–406
8 Brodmann, K. (1909) *Vergleichende Localisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues* Barth
9 Mountcastle, V. B. (1978) in *The Mindful Brain* (Edelman, G. M. and Mountcastle, V. B., eds), pp. 7–50, MIT Press
10 Jones, E. G. (1986) in *Cerebral Cortex, Vol. 5: Sensory-Motor Areas and Aspects of Cortical Connectivity* (Jones, E. G. and Peters, A., eds), pp. 113–183, Plenum Press
11 Gilbert, C. D. (1983) *Annu. Rev. Neurosci.* 6, 217–247
12 Mitani, A. *et al.* (1985) *J. Comp. Neurol.* 235, 430–447
13 Gilbert, C. D. and Wiesel, T. N. (1983) *J. Neurosci.* 3, 1116–1133
14 Rockland, K. S. and Lund, J. S. (1982) *Science* 215, 1532–1534
15 Matsubara, J. A. and Phillips, D. P. (1988) *J. Comp. Neurol.* 268, 38–48
16 Mendelson, J. R. and Cynader, M. S. (1985) *Brain Res.* 327, 331–335
17 Hyvärinen, J. and Poranen, A. (1978) *J. Physiol. (London)* 283, 523–537
18 Warren, S., Hamalainen, H. A. and Gardner, E. P. (1988) *J. Neurophysiol.* 56, 598–622
19 McConnell, S. K. (1988) *Brain Res. Rev.* 13, 1–23
20 McConnell, S. K. (1985) *Science* 229, 1268–1271
21 McConnell, S. K. (1988) *J. Neurosci.* 8, 945–974
22 Peters, A. (1987) in *Cerebral Cortex, Vol. 6: Further Aspects of Cortical Function including Hippocampus* (Jones, E. G. and Peters, A., eds), pp. 267–294, Plenum Press
23 Finlay, B. L. and Pallas, S. L. (1989) *Prog. Neurobiol.* 32, 207–234
24 Rakic, P. (1977) *Philos. Trans. R. Soc. London Ser. B* 278, 245–267
25 Shatz, C. J. and Luskin, M. B. (1986) *J. Neurosci.* 6, 3655–3668
26 Windrem, M. S., Jan de Beur, S. M. and Finlay, B. L. (1986) *Soc. Neurosci. Abstr.* 12, 867
27 Shatz, C. J., Chun, J. J. M. and Luskin, M. B. (1988) in *Cerebral Cortex, Vol. 7: Development and Maturation of Cerebral Cortex* (Peters, A. and Jones, E. G., eds), pp. 35–58, Plenum Press
28 Chun, J. J. M. and Shatz, C. J. (1989) *J. Neurosci.* 9, 1648–1667
29 McConnell, S. K., Ghosh, A. and Shatz, C. J. (1989) *Science* 245, 978–982
30 O'Leary, D. D. M. and Stanfield, B. B. (1989) *J. Neurosci.* 9, 2230–2246
31 Kaas, J. H., Merzenich, M. M. and Killackey, H. P. (1983) *Annu. Rev. Neurosci.* 6, 325–356
32 Sherman, S. M. and Spear, P. D. (1982) *Physiol. Rev.* 62, 738–855
33 Schneider, G. E. (1973) *Brain Behav. Evol.* 8, 73–109
34 Kalil, R. E. and Schneider, G. E. (1975) *Brain Res.* 100, 690–698
35 Devor, M. (1975) *Science* 190, 998–1000
36 Graziadei, P. P. C., Levine, R. R. and Monti-Graziadei, G. A. (1979) *Neuroscience* 4, 713–727
37 Bronchti, G., Heil, P., Scheich, H. and Wollberg, Z. (1989) *J. Comp. Neurol.* 284, 253–274
38 Bronchti, G., Heil, P., Scheich, H. and Wollberg, Z. (1989) in *Neural Mechanisms of Behavior (Proceedings of the 2nd International Congress on Neuroethology)* (Erber, J., Menzel, R., Pflüger, H-J. and Todt, D., eds), p. 147A, Thieme
39 Bronchti, G., Rado, R., Terkel, J. and Wollberg, Z. (1989) in *Neural Mechanisms of Behavior (Proceedings of the 2nd International Congress on Neuroethology)* (Erber, J., Menzel, R., Pflüger, H-J. and Todt, D., eds), p. 201A, Thieme
40 Frost, D. O. (1982) *Dev. Brain Res.* 3, 627–635
41 Frost, D. O. (1984) *J. Comp. Neurol.* 230, 576–592
42 Roe, A. W., Garraghty, P. E. and Sur, M. (1989) *J. Comp. Neurol.* 288, 208–242
43 Vitek, D. J., Schall, J. D. and Leventhal, A. G. (1985) *J. Comp. Neurol.* 241, 1–11
44 Sur, M., Garraghty, P. E. and Roe, A. W. (1988) *Science* 242, 1437–1441
45 Hubel, D. H. and Wiesel, T. N. (1962) *J. Physiol. (London)* 160, 106–154
46 Metin, C. and Frost, D. O. (1989) *Proc. Natl Acad. Sci. USA* 86, 357–361
47 Pallas, S. L., Roe, A. W. and Sur, M. *J. Comp. Neurol.* (in press)
48 Merzenich, M. M., Jenkins, W. M. and Middlebrooks, J. C. (1984) in *Dynamic Aspects of Neocortical Function* (Edelman, G. M., Gall, W. E. and Cowan, W. M., eds), pp. 397–424, Neurosciences Research Foundation
49 Aitken, L. M., Irvine, D. R. F. and Webster, W. R. (1984) in *Handbook of Physiology (Sect. 1: The Nervous System;* Vol. III: *Sensory Processes* Pt 2), pp. 675–737, American Physiological Society
50 Kelly, J. B., Judge, P. W. and Phillips, D. P. (1986) *Hearing Res.* 24, 111–115
51 Phillips, D. P., Judge, P. W. and Kelly, J. B. (1988) *Brain Res.* 443, 281–294
52 Roe, A. W., Pallas, S. L., Hahm, J., Kwon, Y. H. and Sur, M. (1988) *Soc. Neurosci. Abstr.* 14, 460
53 Frost, D. O. and Metin, C. (1985) *Nature* 317, 162–164
54 McKenna, T. M., Weinberger, N. M. and Diamond, D. M. (1989) *Brain Res.* 481, 142–153
55 Sutter, M. L. and Schreiner, C. E. (1989) *Soc. Neurosci. Abstr.* 15, 1116
56 Kaas, J. H. (1983) *Physiol. Rev.* 63, 206–231
57 Jackson, C. A., Peduzzi, J. D. and Hickey, T. L. (1989) *J. Neurosci.* 9, 1242–1253
58 Shatz, C. J. and Luskin, M. B. (1986) *J. Neurosci.* 6, 3655–3668
59 Schneider, G. E. (1981) *Trends Neurosci.* 4, 187–192
60 Walsh, C., Polley, E. H., Hickey, T. L. and Guillery, R. W. (1983) *Nature* 302, 611–614

Acknowledgements

We thank Peter Heil and Henning Scheich for access to unpublished data, Sonal Jhaveri, Gerald Schneider and Paul Katz for their comments on the manuscript, and Teresa Sullivan for assistance with the figures. Our work has been supported by grants from the NIH and the McKnight Foundation.

Brain, Behavior and Evolution
Editor-in-Chief: R. Glenn Northcutt, La Jolla, Calif.

Reprint
Publisher: S. Karger AG, Basel
Printed in Switzerland

Brain Behav. Evol. *31*: 243–251 (1988)

Development and Plasticity of Retinal X and Y Axon Terminations in the Cat's Lateral Geniculate Nucleus

Mriganka Sur

Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Mass., USA

Key Words. Retinogeniculate axons · X cell · Y cell · Terminal arbors · Developmental interactions

Abstract. The technique of injecting single retinogeniculate fibers with horseradish peroxidase enables the terminal arbors of physiologically identified axons to be fully characterized morphologically. We have used this technique to study the postnatal development of retinal X and Y cell arbors within the cat's lateral geniculate nucleus, and the plasticity of these arbors following a variety of manipulations that perturb normal development. These experiments suggest quite specific sequences and mechanisms for the development of individual X and Y retinogeniculate axons. Retinal X axons appear to innervate the lateral geniculate nucleus before Y axons do, and are probably specified innately to their appropriate target lamina A or A1. By 3–4 weeks postnatally, X axons from each eye develop exuberant terminal arbors within the A laminae that by 12 weeks get pruned to the narrow adult form by later developing Y axon arbors from the same eye. The Y arbors progressively expand to form their characteristic broad terminal zones during this period. The laminar location of Y arbors depends on interactions between axons from the two eyes, and their transverse extent on the presence of normal afferent activity in retinogeniculate fibers.

Introduction

The cat's retina contains at least three physiologically and anatomically distinct cell classes: X, Y and W cells [Rodieck, 1979; Lennie, 1980; Sherman and Spear, 1982]. X cells and Y cells each constitute relatively homogeneous populations that can be distinguished from each other along a number of parameters. Retinal X cells have medium-sized somata with small dendritic arbors and medium-caliber axons, and small receptive fields that sum luminance linearly. Y cells have large somata with large dendritic arbors and thick axons, and larger receptive fields that sum luminance nonlinearly. In contrast to X and Y cells, retinal W cells are a rather diverse population. Most W cells have small somata with fine axons, large dendritic arbors and large receptive fields. W cells can be subdivided according to differences in physiological [Rodieck, 1979] or anatomical [Leventhal et al., 1985] features, and different subclasses of these cells may project to different termination zones in the thalamus and midbrain.

X and Y retinal ganglion cells give rise to two pathways that convey information in parallel through the lateral geniculate nucleus to the visual cortex [Hoffmann et al., 1972; So and Shapley, 1979]. Individual X and Y retinal axons have characteristic terminations within the lateral geniculate nucleus (fig. 1, 2), as shown by the method of injecting horseradish peroxidase (HRP) into single, physiologically identified, retinogeniculate axons in the optic tract of adult cats [Bowling and Michael, 1980, 1984; Sur and Sherman, 1982; Sur et al., 1987]. Contralaterally projecting X axons terminate in lamina A, and ipsilaterally projecting axons in lamina A1. X axons have narrow terminal arbors that are about 100 μm wide and contain 500–1,000 terminal boutons (fig. 1). Y axons projecting contralaterally branch to innervate laminae C and A, and those projecting ipsilaterally terminate in lamina A1, in broad, fairly extensive termination zones. Y axon arbors are often 300 μm or so wide and contain 800–2,000 terminal boutons (fig. 2).

Once the normal, adult morphologies of single retinogeniculate arbors are characterized, it is possible

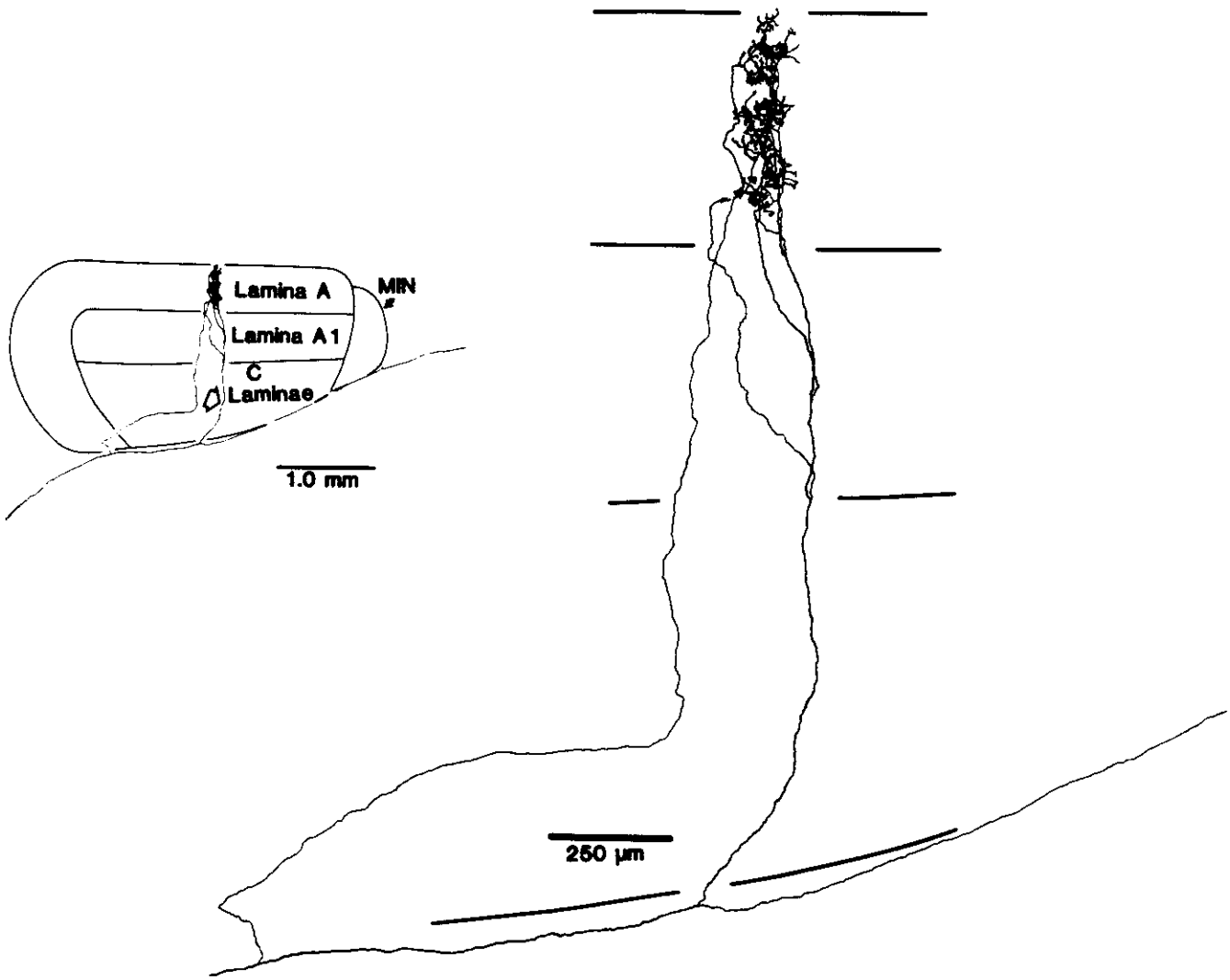

Fig. 1. A retinogeniculate X axon from the right eye of a normal adult cat innervating lamina A of the left lateral geniculate nucleus. The axon had an ON center receptive field that was 0.9° in diameter and was located 9° from the vertical meridian and 2° below the horizontal zero in the right visual field. It was characterized physiologically and injected intracellularly with HRP. The inset to the left shows the injection site (marked with open arrow) on a coronal view of the left lateral geniculate nucleus. The axon was reconstructed from 21 consecutive 100-µm thick serial sections, and the terminal zone in lamina A (containing 793 boutons) from 3 consecutive sections. Apart from the number of terminal boutons, we routinely measured the width and volume of the terminal arbor of all X axons we recovered. MIN: Medial interlaminar nucleus.

to ask how these arbors develop. We have used the intracellular HRP technique to describe: (1) the postnatal development of X and Y axon arbors in kittens, and (2) the plasticity in single axon arbors following a variety of manipulations that perturb normal development. We have compared qualitatively and quantitatively the terminal arbors of X and Y axons in normal adult cats, developing kittens, and adult cats reared with the manipulations described below. These studies then help us to propose specific sequences and mechanisms for the postnatal development of retinal X and Y axon arbors within the lateral geniculate nucleus.

Prenatal Development

It is useful to first review the prenatal development of the cat's retinogeniculate projection, to place the present results on postnatal development in context

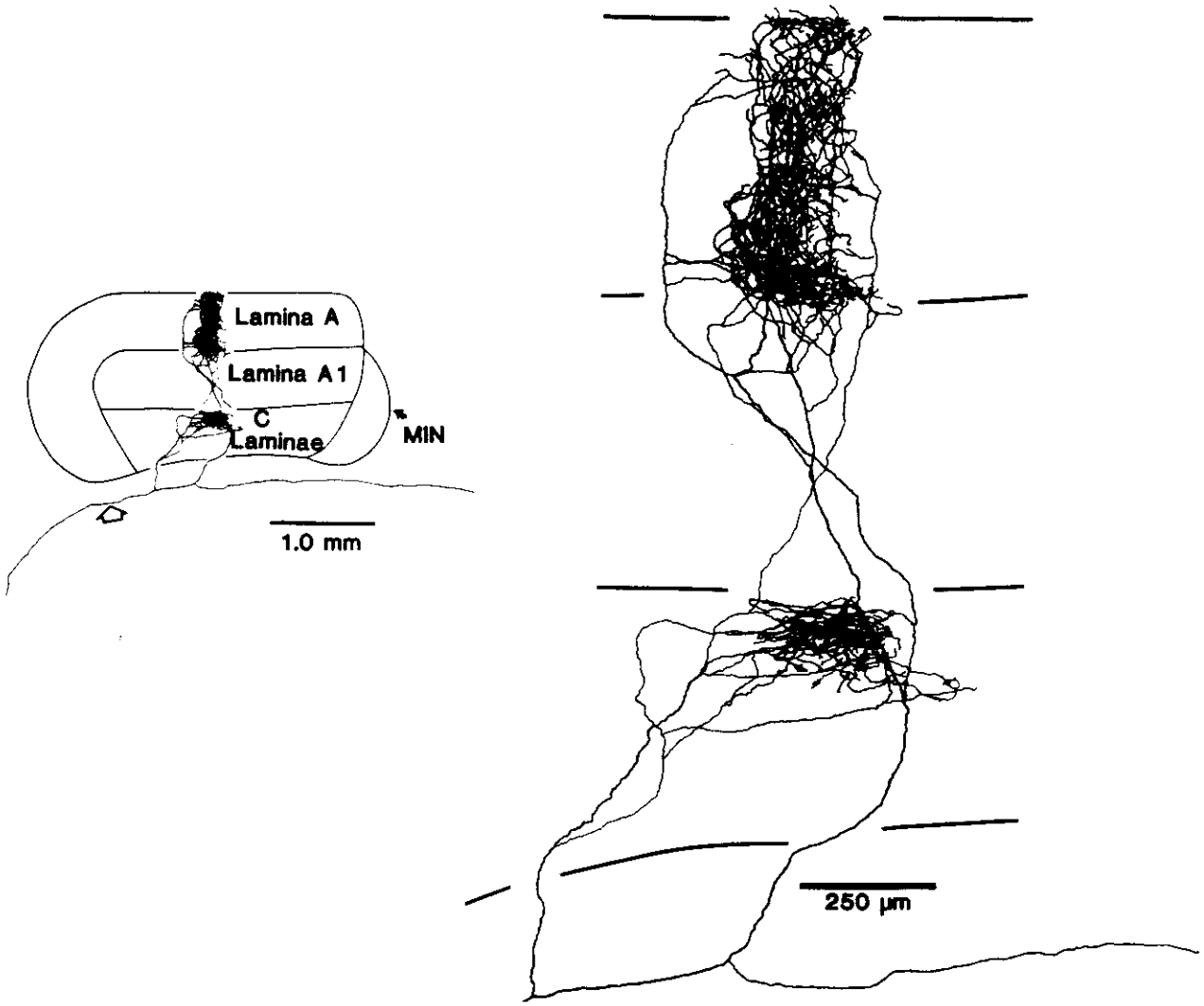

Fig. 2. A retinogeniculate Y axon from the right eye of a normal adult cat innervating laminae C and A of the left lateral geniculate nucleus. The axon had an OFF center receptive field that was 1.2° in diameter and was located 11.5° from the vertical midline and 3.5° below the horizontal zero in the right visual field. The inset to the left shows the injection site (marked with open arrow) on a coronal view of the left lateral geniculate nucleus. The axon was reconstructed from 27 consecutive 100-µm thick serial sections, and the terminal zone in lamina A (containing 1,405 boutons) from 6 consecutive sections. We routinely counted the number of boutons and measured the widths and volumes of terminal arbors for our recovered Y axons. MIN: Medial interlaminar nucleus.

[see also Shatz and Sretavan, 1986]. Three major events can be identified in prenatal retinogeniculate development.

(1) In the retina, medium-sized cells (presumably X cells) are generated first, starting in the central retina at embryonic day 23 (E23; kittens are born at approximately E63), followed by large cells (presumably Y cells). Small cells (presumably W cells) are generated throughout the period of cell division, and many of these cells are the last ganglion cells born in the retina [Walsh et al., 1983; Walsh and Polley, 1985]. Fiber ingrowth into the optic nerve and tract follows a similar pattern [Guillery et al., 1982; Walsh et al., 1983]. The oldest, medium-caliber axons lie farthest from the pia, large fibers lie nearer the pia, and many of the smallest fibers are nearest the pia.

(2) Numbers of retinal ganglion cells and their axons in the optic nerve increase rapidly until E39 [Williams et al., 1982; this may extend to E45, Ng and Stone, 1982] and then decline, first rapidly and then

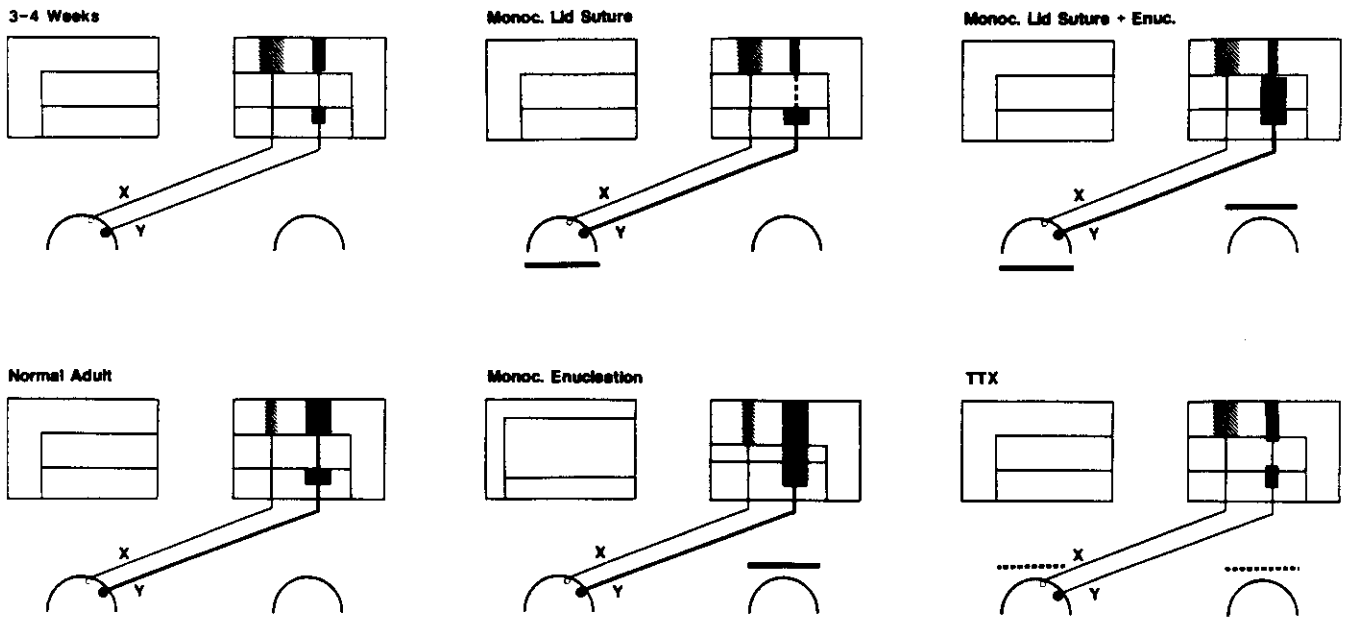

Fig. 3. Summary of retinogeniculate terminations in normal 3- to 4-week-old kittens and normal adult cats, as well as in cats reared with monocular lid suture, monocular enucleation, monocular lid suture of one eye plus enucleation of the other, and binocular retinal impulse blockade with tetrodotoxin (TTX). Each schematic shows the two eyes and two lateral geniculate nuclei, with retinogeniculate X and Y axons from the left eye projecting contralaterally to the right lateral geniculate nucleus. Each lateral geniculate nucleus contains laminae A, A1 and C, as shown also in figure 1 and 2. The normal postnatal development of X and Y axon arbors within the A laminae, and the inter- and intralaminar plasticity of arbors following manipulations that perturb development, are indicated in the figure and described further in the text.

more gradually to reach adult numbers by the 4th to 6th postnatal week.

(3) In the lateral geniculate nucleus, projections from the two eyes initially overlap, with maximum overlap seen around E45 [Shatz, 1983; Chalupa and Williams, 1984b]. Axons from the two eyes then start to segregate into eye-specific laminae, so that by birth the adult pattern of laminar organization is seen in the nucleus. During the prenatal overlap period, retinogeniculate fibers have simple morphologies and are relatively restricted in extent [Sretavan and Shatz, 1984, 1986]. Reduction in overlap occurs by loss of a limited number of minor branches that lie in inappropriate laminae, and laminar development by selective growth within appropriate eye-specific regions of the lateral geniculate nucleus. Reduction in overlap may also occur by loss of retinogeniculate axons that project to inappropriate regions of the nucleus [Sherman, 1985]; however, the bulk of axonal loss occurs before laminar segregation begins [Williams et al., 1982]. At birth, retinogeniculate axons have narrow terminal arbors that are approximately 80–100 μm in width [Sretavan and Shatz, 1986], but it is not possible to physiologically separate them into X or Y axons at this stage.

Postnatal Development of X and Y Retinogeniculate Axons

Postnatally, the earliest age at which retinal ganglion cells and retinogeniculate axons can be physiologically classified as X or Y cell is 3–4 weeks after birth [Hamasaki and Flynn, 1977; Hamasaki and Sutija, 1979; Sur et al., 1984; Friedlander et al., 1985]. At this age, many retinogeniculate axonal branches terminate in growth cones or filopodia [Mason, 1982; Sur et al., 1984], but the laminar location and extent of terminal arbors is still quite clear. X axons at 3–4 weeks of age have fairly extensive terminal zones in lamina A or A1 that are *wider* or more extensive than in the adult (fig. 3) [Sur et al., 1984]. These terminal

zones progressively narrow over the next 8 weeks, so that by 12 weeks the adult extent of terminal arbors is achieved [Sur et al., 1984]. By 12 weeks, the terminal boutons on X axon arbors are also well formed and have the clumped appearance characteristic of adult X axon terminals.

In contrast to the progressive *reduction* in X axon arbors from 3–4 to 12 weeks, Y axon arbors *expand* during this period [Friedlander et al., 1985; Sur et al., 1984]. Thus Y axons in 3- to 4-week-old kittens are much narrower than in adults (fig. 3), and these arbors progressively grow larger in extent through 12 weeks and even beyond. The complementary development of X and Y axon terminations suggested to us that these arbors are shaped by interactions between X and Y axons from the same eye during development. We hypothesized that X axons from one eye invade the lateral geniculate nucleus before Y axons do and develop exuberant terminal arbors in the A laminae that get pruned as the later-developing Y axons from the same eye expand their terminal arbors in the A laminae. Some of the experiments on plasticity of retinogeniculate terminations described below are designed to test this hypothesis of interactions between X and Y axons from the *same* eye during development. Other experiments are designed to study the interactions between axons from the *two* eyes during development. The experiments together enable us to propose specific mechanisms for the development of the laminar locations and sizes of retinogeniculate X and Y axon arbors.

Plasticity of X and Y Axon Arbors

Monocular Lid Suture

Suturing the lids of one eye from birth to adulthood has profound consequences on the physiology and morphology of cells in the lateral geniculate nucleus. Y cells are recorded in significantly fewer numbers in deprived laminae [Sherman et al., 1972; see for review Sherman and Spear, 1982], and cells in these laminae have smaller somata in the binocular segment [Guillery, 1972a; Wiesel and Hubel, 1963]. Many Y cells have abnormal morphologies, and some X cells have morphology typical of Y cells [Friedlander et al., 1982], suggesting that some cells that would normally receive Y cell input now accept and retain X cell input. At least some of these effects may be due to the fact that Y cells are generated later in the retina than X cells, the development of the Y cell pathway may lag the X cell pathway, and the Y cell pathway may thus be much more susceptible to postnatal manipulations such as lid suture (see below).

When we examined the retinogeniculate arbors of X and Y axons in adult cats raised with monocular lid suture from birth, we found that Y axon terminations in the A laminae were severely reduced compared to normal adult arbors (fig. 3) [Sur et al., 1982]. Many contralaterally projecting Y axons, that in normal adult cats innervate both laminae C and A, now innervated only lamina C and did not innervate lamina A at all. Y axon terminations in lamina C were normal. At the same time, many X axon arbors (in the A laminae) were larger than those in normal adult cats. The widths of both the expanded X axon arbors and reduced Y axon arbors in the A laminae were statistically different from those in normal adult cats, and the arbors in monocularly sutured cats appeared similar to X and Y axon arbors in 3- to 4-week-old kittens. These results suggest that X and Y axons from the same eye indeed interact with each other during development, perhaps for synaptic space on cells in the A laminae of the lateral geniculate nucleus. Thus, the expanding Y arbors, which would normally prune the exuberant X arbors in the A laminae, are now placed at a disadvantage due to the lid suture and fail to prune the X arbors which then remain exuberant. In regions where X arbors are not present, such as the C lamina, Y arbors develop normally. Consistent with this hypothesis is the result that in the deprived A laminae of monocularly sutured cats, X axon arbors contact cells that they may not normally contact (that is, cells with morphology typical of Y cells), and many Y cells in the deprived A laminae have abnormal morphologies [Friedlander et al., 1982; see, however, Weller and Humphrey, 1985].

We next asked how axons from the two eyes interact in shaping terminal arbors within the lateral geniculate nucleus.

Neonatal Monocular Enucleation

We examined retinogeniculate axon morphologies in cats that were raised with one eye enucleated within 1 day after birth [Garraghty et al., 1986b]. Neonatal monocular enucleation leads to sprouting of some retinogeniculate fibers from the remaining eye into the denervated lamina(e) [Guillery, 1972b; Hickey, 1975; Robson et al., 1978]. We wondered whether both X and Y axons from the remaining eye gave rise to

translaminar sprouts or whether sprouting by some axons had any effect on the morphology of axons that did *not* sprout. We found that X axons from the remaining eye were always restricted to lamina A or A1 appropriate to their eye of origin whereas Y axons sprouted into the denervated lamina(e). For example, contralaterally projecting X axons always projected to, and remained confined to, lamina A, while contralaterally projecting Y axons projected not only to laminae C and A but also sprouted into lamina A1 (fig. 3). Furthermore, X axon arbors had more terminal boutons than in normal adult cats and were larger in terminal volume than normal, suggesting that they retained their immature exuberance into adulthood, perhaps as a result of the Y arbors preferring to sprout into denervated territory and thus failing to prune the X arbors.

The sprouting of Y axons, for example the sprouting of contralaterally projecting Y axons through denervated lamina A1, created another lamina in addition to lamina C where there were only Y axon terminations and no X axon terminations. If now monocular lid suture were added to the enucleation (that is, if one eye were removed at birth and the other eye sutured), we could test further the hypothesis that development of X and Y axon arbors involved pruning of X arbors by Y arbors. If contralaterally projecting Y axon arbors, for example, were reduced in all laminae including the sprouted lamina A1, it would suggest that Y axon arbors developed independently of X arbors. If, on the other hand, (1) contralaterally projecting Y arbors were reduced only in lamina A innervated normally by the remaining eye (to which X axons also projected), but remained extensive in the sprouted lamina A1 as well as in normally innervated lamina C (to both of which X axons did not project), and (2) a reduction in Y arbor extent and bouton number in lamina A compared to normal would be paralleled by an increase in X arbor extent and bouton number, as observed in deprived lamina A or A1 in monocularly sutured cats, (see above), it would provide further evidence that the development of X and Y arbors involved interactions between the two cell classes. The latter, indeed, is what our results clearly indicate [Garraghty et al., 1986a]. Considering contralaterally projecting axons, for example, Y axon arbors in lamina A are much smaller than in normal cats or in monocularly enucleated cats without lid suture of the remaining eye, but their terminations in lamina C as well as their sprouted terminations in lamina A1 are extensive in terminal size and bouton number (fig. 3). At the same time, X axon arbors in lamina A (or in lamina A1) are larger in terminal volume and bouton number compared to normal. The results in lamina A for contralaterally projecting axons, or in lamina A1 for ipsilaterally projecting axons, are thus very similar to those in monocularly sutured cats where the other eye is open.

Why do X axons from the remaining eye not sprout through the denervated laminae? There are two possibilities here: either the enucleation is not done early enough and by birth X axons are already past their 'critical period' for dramatic arbor growth, or there are intrinsic differences between X and Y axons such that only Y axons possess the capacity to sprout and X axons always remain confined to their appropriate target lamina. To distinguish between these possibilities, we have studied cats that were monocularly enucleated prenatally.

Prenatal Monocular Enucleation

The first group of cats we have studied has been adult cats that had one eye removed at E44. At this age, overlap of fibers from the two eyes is maximal in the lateral geniculate nucleus [Shatz, 1983], and we reasoned that, if indeed the shaping of retinogeniculate arbors involved significant interactions between afferents from the two eyes, the effect of eye removal on terminal arbors should be pronounced at this age.

Following monocular enucleation at E44, eye-specific laminae do not develop in the lateral geniculate nucleus. The nucleus has only two histologically demarcable zones, a broad 'magnocellular' zone in the dorsal part separated by an interlaminar plexus from a narrow ventral 'parvocellular' zone. The magnocellular zone probably represents laminae A, A1 and dorsal C collapsed together, and the parvocellular zone probably represents the ventral C laminae [Garraghty et al., 1987b; cf. Chalupa and Williams, 1984a]. We find a striking difference between the terminal arbors of X and Y axons in these cats [Sretavan et al., 1985; Garraghty et al., 1987b]. X axons from the remaining eye appear to always terminate in territory appropriate to their eye of origin, as if laminae A or A1 were present. That is, X axons projecting contralaterally terminate in the dorsal third of the nucleus, where lamina A would have been, and X axons projecting ipsilaterally terminate in the middle third, where lamina A1 would have been. In contrast, most Y axons from the remaining eye (projecting either

contralaterally or ipsilaterally) show extensive terminations throughout the magnocellular portion of the nucleus, as if they sprouted through laminae A, A1 and dorsal C. We have also recovered one contralaterally projecting Y axon that has its terminal arbor restricted to the middle tier only, where lamina A1 would have been, and one ipsilaterally projecting Y axon that is restricted to the outer tier, where lamina A would have been. These axons possibly represent axons that would have either retracted or died if the other eye were present but survive now.

While these experiments do not conclusively demonstrate that X axons never sprout into inappropriate territory (cats with even earlier ages of enucleation would be needed here), our results do suggest that there are indeed intrinsic differences between retinogeniculate X and Y axons that determine the laminar location of their arbors. X axons from each eye appear to be innately specified to their appropriate target lamina A or A1 independent of the other eye. Y axons from one eye need the laminar specificity established by the other eye (presumably by the earlier born X axons) to know when to stop growing, and in the absence of such preestablished laminar specificity sprout into regions normally inappropriate for their eye of origin.

Blockade of Retinal Impulse Activity

In the final experiment in this series, we asked what features of axons from one eye indicate to Y axons from the other eye when to stop growing across their appropriate lamina. Furthermore, we wished to study the role of afferent impulse activity in development, and distinguish this from physical removal of an eye or even disruption of light through monocular lid suture, binocular lid suture [Uhlrich et al., 1986] or dark-rearing [Garraghty et al., 1987a]. As described above, the effects of monocular lid suture on retinogeniculate arbors differ from those of monocular enucleation: monocular lid suture from birth does not cause Y axons from the nondeprived eye to sprout into deprived laminae, whereas monocular enucleation at birth causes Y axons from the remaining eye to sprout into deafferented laminae. However, Y arbors in deprived lamina A or A1 in monocularly sutured cats are much reduced compared to normal, and X arbors are correspondingly larger.

We examined retinogeniculate X and Y axon arbors in cats reared with binocular blockade of retinal impulse activity from 2 to 10 weeks after birth, and in cats reared with monocular blockade from birth to 8–10 weeks [Sur et al., 1985]. The blockade was produced by regular, repeated intraocular injections of tetrodotoxin in doses known to block impulse activity but not cause systemic toxicity [Stryker and Harris, 1986]. In monocularly blocked animals, we found that contralaterally projecting Y axons from the normal eye sprouted terminations into blocked lamina A1, just as contralaterally projecting Y axons from the remaining eye do in monocularly enucleated cats. X axons from the normal eye appeared qualitatively normal in these cats. We have not yet recovered significant numbers of axons from the blocked eye in monocularly blocked animals.

In binocularly blocked animals, we found that Y axons (from either, blocked, eye) sprouted slightly into adjacent laminae (fig. 3). At the same time, the normal development of both X and Y arbor *within* lamina A or A1 seemed to be arrested, and the arbors seemed similar to those in very young normal kittens or in deprived lamina A or A1 in monocularly sutured cats reared to adulthood. Thus, Y arbors in the A laminae of binocularly blocked animals were much smaller than in normal animals at the same age but comparable to Y arbors in normal 3- to 4-week-old kittens, while X arbors in the binocularly blocked animals were broader than in normal animals at the same age but similar to X arbors in 3- to 4-week-old kittens (fig. 3). Furthermore, the size and density of terminal boutons on both X and Y axons were very immature in binocularly blocked animals. These results suggest that a necessary prerequisite for the normal development of retinogeniculate arbors (both the interlaminar restriction as well as the intralaminar shaping of X and Y axons) is electrical activity in the two eyes.

Mechanisms of Retinogeniculate Development

What mechanisms do these experiments suggest for the normal development of retinogeniculate X and Y axons, and how do these mechanisms in turn explain the plasticity that we observe in X and Y arbors after manipulations that perturb normal development?

We can propose, at the level of testable hypotheses, both the sequel of normal development and the factors that shape X and Y axon arbors in the A laminae. The sequel of prenatal and postnatal events in reti-

nogeniculate development suggested by our data (in conjunction with other data reviewed earlier) is the following. X cells are born earlier in the retina than Y cells, and X axons innervate the lateral geniculate nucleus earlier. Their axons develop arbors that are, at least for the most part, confined to the appropriate location for lamina A or A1 within the nucleus. Between birth and 3–4 weeks postnatally, X axons develop exuberant arbors within lamina A or A1 that get pruned by Y axon arbors in these laminae.

The factors that shape X and Y axon arbors in the A laminae are the following. The laminar location or dorsoventral height of X arbors appears to be specified innately, perhaps through axon-target interactions or target-mediated substrates in the lateral geniculate nucleus. No manipulation we have done has changed the laminar specificity of X axons. The transverse extent or width of X axons in the A laminae is determined by interactions with Y axon arbors from the same eye. Manipulations that cause Y arbors in lamina A or A1 to remain small (monocular lid suture with or without enucleation of the other eye, and retinal impulse blockade) lead to expanded X axon arbors (that is, X arbors with retained immature exuberance) in the same lamina. The laminar location or dorsoventral height of Y axon arbors from one eye seems to depend most critically on interactions with axons from the other eye. When one eye is enucleated or its electrical activity blocked, Y axons from the other eye sprout into the deafferented or blocked lamina. The transverse extent or width of Y arbors in the A laminae perhaps depends simply on normal afferent activity in the retinogeniculate fibers. Manipulations that impede normal activity such as monocular lid suture (with the other eye open or enucleated), and total impulse blockade, all lead to abnormally small Y axon arbors in deprived or blocked lamina A or A1. It should be emphasized that these remain hypotheses about the mechanisms of retinogeniculate development at the level of single fibers from physiologically distinct retinal cell classes, and these hypotheses may have to be modified or altered as future experiments dictate.

Acknowledgments

I thank Anna Roe and Preston Garraghty for their comments on the manuscript. Supported by NIH grant EY 07023, the Sloan Foundation and the Whitaker Health Sciences Fund.

References

Bowling, D.B.; Michael, C.R.: Projection patterns of single physiologically characterized optic tract fibers in cat. Nature *286:* 899–902 (1980).

Bowling, D.B.; Michael, C.R.: Terminal patterns of single, physiologically characterized optic tract fibers in the cat's lateral geniculate nucleus. J. Neurosci. *4:* 198–216 (1984).

Chalupa, L.; Williams, R.W.: Organization of the cat's lateral geniculate nucleus following interruption of prenatal binocular competition. Hum. Neurobiol. *3:* 103–107 (1984a).

Chalupa, L.; Williams, R.W.: Prenatal development and reorganization in the visual system of the cat; in Stone, Dreher, Rapaport, Development of visual pathways in mammals, pp. 89–102 (Liss, New York 1984b).

Friedlander, M.J.; Martin, K.A.C.; Vahle-Hinz, C.: The structure of the terminal arborizations of physiologically identified retinal ganglion cell Y axons in the kitten. J. Physiol. *359:* 293–313 (1985).

Friedlander, M.J.; Stanford, L.R.; Sherman, S.M.: Effects of monocular deprivation on the structure/function relationship of individual neurons in the cat's lateral geniculate nucleus. J. Neurosci. *2:* 321–330 (1982).

Garraghty, P.E.; Frost, D.O.; Sur, M.: The morphology of retinogeniculate X- and Y-cell axons in dark-reared cats. Exp. Brain Res. *66:* 115–127 (1987a).

Garraghty, P.E.; Shatz, C.J.; Sretavan, D.; Sur, M.: Prenatal monocular enucleation in the cat: effects on the morphology of retinogeniculate axons and formation of laminae in the lateral geniculate nucleus. Investve Ophthal. vis. Sci., suppl. *28:* 335 (1987b).

Garraghty, P.E.; Sur, M.; Sherman, S.M.: The role of competitive interactions in the postnatal development of X and Y retinogeniculate axons. J. comp. Neurol. *251:* 216–239 (1986a).

Garraghty, P.E.; Sur, M.; Weller, R.E.; Sherman, S.M.: The morphology of retinogeniculate X and Y axon arbors in monocularly enucleated cats. J. comp. Neurol. *251:* 198–215 (1986b).

Guillery, R.W.: Binocular competition in the control of geniculate cell growth. J. comp. Neurol. *144:* 117–130 (1972a).

Guillery, R.W.: Experiments to determine whether retinogeniculate axons can form translaminar collateral sprouts in the dorsal geniculate nucleus of the cat. J. comp. Neurol. *146:* 407–420 (1972b).

Guillery, R.W.; Polley, E.H.; Torrealba, F.: The arrangement of axons according to fiber diameter in the optic tract of the cat. J. Neurosci. *2:* 714–721 (1982).

Hamasaki, D.I.; Flynn, J.T.: Physiological properties of retinal ganglion cells of 3-week-old kittens. Vision Res. *17:* 275–284 (1977).

Hamasaki, D.I.; Sutija, V.G.: Development of X- and Y-cells in kittens. Exp. Brain Res. *35:* 6–23 (1979).

Hickey, T.L.: Translaminar growth of axons in the kitten dorsal lateral geniculate nucleus following removal of one eye. J. comp. Neurol. *161:* 359–382 (1975).

Hoffmann, K.-P.; Stone, J.; Sherman, S.M.: Relay of receptive-field properties in dorsal lateral geniculate nucleus of the cat. J. Neurophysiol. *35:* 518–531 (1972).

Lennie, P.: Parallel visual pathways. Vision Res. *20:* 561–594 (1980).

Leventhal, A.G.; Rodieck, R.W.; Dreher, B.: Central projections of cat retinal ganglion cells. J. comp. Neurol. *237:* 216–226 (1985).

Mason, C.A.: Development of terminal arbors of retino-geniculate axons in the kitten. I. Light microscopical observations. Neuroscience *7:* 541–559 (1982).

Ng, A.Y.K.; Stone, J.: The optic nerve of the cat: appearance and loss of axons during normal development. Devl Brain Res. *5:* 263–271 (1982).

Robson, J.A.; Mason, C.A.; Guillery, R.W.: Terminal arbors of axons that have formed abnormal connections. Science *201:* 635–637 (1987).

Rodieck, R.W.: Visual pathways. Annu. Rev. Neurosci. *2:* 193–225 (1979).

Shatz, C.J.: The prenatal development of the cat's retinogeniculate pathway. J. Neurosci. *3:* 482–499 (1983).

Shatz, C.J.; Sretavan, D.W.: Interactions between retinal ganglion cells during the development of the mammalian visual system. Annu. Rev. Neurosci. *9:* 171–207 (1986).

Sherman, S.M.: Development of retinal projections to the cat's lateral geniculate nucleus. Trends Neurosci. *8:* 350–355 (1985).

Sherman, S.M.; Hoffmann, K.P.; Stone, J.: Loss of a specific cell type from the dorsal lateral geniculate nucleus in visually deprived cats. J. Neurophysiol. *35:* 532–541 (1972).

Sherman, S.M.; Spear, P.D.: Organization of visual pathways in normal and visually deprived cats. Physiol. Rev. *62:* 738–855 (1982).

So, Y.T.; Shapley, R.: Spatial properties of X and Y cells in the lateral geniculate nucleus of the cat and conduction velocities of their inputs. Exp. Brain Res. *36:* 533–550 (1979).

Sretavan, D.W.; Garraghty, P.E.; Sur, M.; Shatz, C.J.: Development of retinogeniculate axon arbors following prenatal unilateral enucleation. Soc. Neurosci. Abstr. *11:* 805 (1985).

Sretavan, D.W.; Shatz, C.: Prenatal development of retinal ganglion cell axons: segregation into eye-specific layers within the cat's lateral geniculate nucleus. J. Neurosci. *6:* 234–251 (1986).

Sretavan, D.W.; Shatz, C.: Prenatal development of individual retinogeniculate axons during the period of segregation. Nature *308:* 845–848 (1984).

Stryker, M.P.; Harris, W.A.: Binocular impulse blockade prevents the formation of ocular dominance columns in cat visual cortex. J. Neurosci. *6:* 2117–2133 (1986).

Sur, M.; Esguerra, M.; Garraghty, P.E.; Kritzer, M.F.; Sherman, S.M.: Morphology of physiologically identified retinal X- and Y-cell axons in the cat lateral geniculate nucleus. J. Neurophysiol. *58:* 1–32 (1987).

Sur, M.; Garraghty, P.E.; Stryker, M.P.: Morphology of physiologically identified retinogeniculate axons in cats following blockade of retinal impulse activity. Soc. Neurosci. Abstr. *11:* 805 (1985).

Sur, M.; Humphrey, A.L.; Sherman, S.M.: Monocular deprivation affects X- and Y-cell retinogeniculate terminations in cats. Nature *300:* 183–185 (1982).

Sur, M.; Sherman, S.M.: Retinogeniculate terminations in cats: morphological differences between X- and Y-cell axons. Science *218:* 389–391 (1982).

Sur, M.; Weller, R.E.; Sherman, S.M.: Development of retinogeniculate X- and Y-cell terminations in kittens. Nature *310:* 246–249 (1984).

Uhlrich, D.J.; Raczkowski, D.; Sherman, S.M.: Axonal termination patterns in the lateral geniculate nucleus of retinal X- and Y-cells in cats raised with binocular lid suture. Soc. Neurosci. Abstr. *12:* 439 (1986).

Walsh, C.; Polley, E.H.: The topography of ganglion cell production in the cat's retina. J. Neurosci. *5:* 741–750 (1985).

Walsh, C.; Polley, E.H.; Hickey, T.L.; Guillery, R.G.: Generation of cat retinal ganglion cells in relation to central pathways. Nature *302:* 611–614 (1983).

Weller, R.E.; Humphrey, A.L.: Structural correlates of functional subgroups among X-cells in the cat LGN. Soc. Neurosci. Abstr. *11:* 318 (1985).

Wiesel, T.N.; Hubel, D.H.: Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. J. Neurophyisol. *26:* 978–993 (1963).

Williams, R.W.; Bastiani, M.J.; Lia, B.; Chalupa, L.M.: Growth cones, dying axons, and developmental fluctuations in the fiber population of the cat's optic nerve. J. comp. Neurol. *246:* 32–69 (1982).

Dr. Mriganka Sur
Department of Brain and Cognitive Sciences
MIT, E25-618
Cambridge, MA 02139 (USA)

Mriganka Sur
Massachusetts Institute of Technology
Cambridge, MA 02139
U.S.A.

THE SOMATOSENSORY SYSTEM

1. RECEPTORS

Receptors in the skin can be classified both according to the morphology of their endings and by their physiological responses to deformation. Specific receptors subserve specific sub-modalities of somatic sensation.

Slowly adapting (SA) receptors, as their name suggests, respond in tonic fashion to a maintained indentation. They convey information about static touch or pressure. SA type I receptors are the Merkel cell- neurite complex. SA type II receptors are Ruffini endings.

Rapidly adapting (RA) receptors respond phasically to maintained indentation, to its onset and offset. They respond well to oscillatory stimuli of varying depth, and convey information about flutter-vibration. Low frequency transduction in the glabrous skin is done by Meissner corpuscles, and in hairy skin by nerve endings in the hair follicle complex. High frequency transduction, in both glabrous and hairy skin, is done by the deep-lying Pacinian corpusles.

In muscles, spindle afferents with annulospiral endings provide information about muscle length. Golgi tendon organs signal muscle tension. In joint capsules, Ruffini endings signal joint angle. Together, these receptors provide information on limb position or kinesthesis.

The various kinds of encapsulated endings above are connected to large diameter, heavily myelinated, primary afferent fibers. Somatic transduction can also be done by free nerve endings on small diameter, lightly myelinated or unmyelinated primary afferent fibers. Afferent fibers are bundled in nerves, and information from a dermatome on the skin enters the appropriate level of the spinal cord.

2. ASCENDING PATHWAYS

There are two major pathways that carry somatic information through the spinal cord. In addition, the trigeminal system conveys somatic information from the face and part of the head.

A. The dorsal column - medial lemniscal system (touch-pressure, flutter-vibration and kinesthesis). Large diameter primary afferents project ipsilaterally via the dorsal columns to the nucleus gracilis (lower body) and cuneatus (upper body); collaterals enter the dorsal horn to relay to spinal reflex pathways, spinocerebellar neurons and some spinothalamic and spinoreticular neurons. Fibers representing different submodalities terminate

in different parts of the dorsal column nuclei (DCN). The dorsal column nuclei project to the contralateral thalamus - principally to the ventroposterolateral nucleus. (VPL). After leaving the DCN, the ascending axons cross the midline as internal arcuate fibers in the medulla and ascend toward the thalamus in the medial lemniscus.

B. The anterolateral system (touch, pain and temperature). Small diameter primary afferents project via Lissauer's tract to dorsal horn neurons, principally ipsilateral to the side of entry. Collaterals relay to spinal reflex pathways, and to spinoreticular, spinocervical and spinothalamic neurons.

Axons ascending toward the thalamus (spinothalamic tract fibers) are principally crossed and traverse the midline over several segments above their cells of origin. The cells of origin are found mainly in layers III-V of the spinal gray matter. Spinothalamic tract axons ascend in the anterolateral funiculus and terminate in several regions of the brain including a) the VPL nucleus of the thalamus b) the centrolateral intralaminar nucleus of the thalamus, c) the posteromedial nucleus (Pom) of the thalamus, d) various brain stem nuclei, e) the periaqueductal gray matter of the midbrain. Thus, some axons in the spinothalamic tract may send out collaterals en route to the thalamus, while others may never reach the thalamus.

C. The trigeminal system. The organization of this system is analogous to that of the segmental system ascending via the spinal cord. The primary afferents are found principally in cranial nerve V, also in nerves VII, IX, and X.

Thick, myelinated primary afferents for touch and vibration have cell bodies located in the semilunar ganglion and send a major axonal branch into the principal sensory nucleus of the V nerve, the functional equivalent of the dorsal column nuclei. Collaterals descend in the spinal tract of V to all regions of the spinal nucleus of V (particularly the magnocellular region of the caudal division) to synapse with cells projecting to the cerebellum and with "spinothalamic - like" cells.

The principal nucleus of V sends to the thalamus crossed axons (ventral trigeminothalamic tract) that ascend in association with the medial lemniscus and uncrossed axons (dorsal trigeminothalamic tract) that ascend near the central gray. These axons terminate principally in the ventroposteromedial nucleus (VPM), with a few going on to Pom.

Primary afferents for position sense (joint and muscle afferents) have cell bodies located in the mesencephalic nucleus of V. Primary afferents and interneurons of the nucleus send axons to the motor nucleus of V for masticatory reflexes. Cells of the mesencephalic nucleus of V also project to the cerebellum and perhaps to thalamus.

Smaller diameter primary afferents for pain and temperature have cell bodies located in the semilunar ganglion and send axons into the spinal tract of V. They descend to terminate mainly in the substantia gelatinosa of the caudal division of the spinal nucleus of V. The axons of the second order neurons ascend with the contralateral medial lemniscus and project to VPM, Pom and the intralaminar thalamic nuclei. They also send collaterals to the brain

stem and midbrain.

3. THE SOMATOSENSORY THALAMUS

An important aspect of organization of the somatosensory thalamus is the segregation of input from different receptor classes within nuclei and sub-nuclei. The thalamocortical projection is thus a highly parallel input to cortex.

Touch and vibration information is carried by axons originating in the dorsal column nuclei and the principal nucleus of V to central parts of VPL and VPM. In at least VPL, there is a segregation of neurons that represent different types of receptors. Information originating from stretch receptors is carried (by axons originating in DCN) to the ventral posterior oral nucleus (VPO), just rostral to VPL and VPM. Information originating from deep structures (joints, fascia, periosteum) is carried by axons originating in the DCN to the ventral posterior superior nucleus (VPS), just dorsal to VPL and VPM.

Temperature and pain information is relayed by axons of the spinothalamic tract and from the caudal division of the spinal trigeminal nucleus to perhaps the rostral and caudal extermities of VPL and VPM, and to Pom.

4. SOMATOSENSORY CORTEX

The somatosensory cortex of the postcentral gyrus in monkeys, known earlier as "SI," consists of 4 different cytoarchitectonic areas that form medial-lateral oriented bands of tissue. Each area represents principally one modality and gets input from corresponding parts of the ventral posterior nuclear complex (VPL, VPM, VPO, VPS). These areas and the inputs they receive are:

(a) area 3a - stretch receptors from muscle; input from VPO.
(b) area 3b - cutaneous receptors; input from VPL and VPM (more numerous slowly adapting receptors than areas 3b; no Pacinian input).
(c) area 1 - cutaneous receptors; input from VPL and VPM (less numerous slowly adapting receptors than area 3b; includes Pacinian input).
(d) area 2 - cutaneous input from areas 3b and 1, and thalamic input from VPS (receptors from deep structures - joints, fascia, periosteum).

Some VPL neurons project to both areas 3b and 1; some neurons project only to area 1 or only to area 3b. There are 4 separate body representations in the postcentral cortex, one in each cytoarchitectonic area (3a, 3b, 1, 2). The cutaneous representations in areas 3b and 1 are particularly well defined. The representations cannot be described as a "homunculus." Within area 3b, a modular segregation of neurons receiving input from slowly adapting and rapidly adapting cutaneous receptors can be distinguished.

The maps of the skin surface in cortex are not static entities but are dynamic, subect to use-dependent changes throughout life, including adulthood.

The "SII" region in the monkey, in the parietal operculum on the upper and

inner banks of the Sylvian sulcus, consists of several different cortical areas. "SII proper" receives input from the postcentral "SI" region and from the ventroposterior complex of the thalamus. The region caudal to this receives input from the posteromedial nucleus (Pom) of the thalamus and may be important in the conscious perception of pain.

5. PAIN

A. Receptors

a. Most if not all pain receptors are free nerve endings that, when activated by stimuli that have the potential to damage tissue, evoke sensations of pain.

b. Superficial pain, from the skin: the first sensation of "pricking pain" is well localized, of short duration, and is mediated by A fibers. The second sensation of "burning pain" is less localized, more prolonged, and is mediated by C fibers.

c. Deep pain, from muscles, bones, joints, or connective tissue has a diffuse aching character and is served by both A and C fibers.

d. Itch is served by C fibers and can be evoked by a variety of externally applied stimuli (mechanical, chemical) or by intradermal release of chemical mediators such as histamines.

B. Central Projections

a. Primary pain afferents enter the dorsal root, bifurcate and ascend and descend for 1 - 3 segments in Lissauer's tract, and terminate largely in lamina I and the substantia gelatinosa. Neurons in other laminae can extend their dentrites into these laminae and hence can receive pain input as well.

b. Second order cells project through the spinothalamic tract (see earlier section on anterolateral system).

c. The gate-control hypothesis for pain suggests that small diamater pain fibers and large diameter touch fibers have antagonistic effects on cells in the substantia gelatinosa. These cells in turn project to and regulate the firing of cells deeper in the dorsal horn. Activity in pain fibers keeps the gate open while activity in touch fibers closes the gate. Recent evidence suggests that this hypothesis needs to be modified.

C. Descending Control of Pain Transmission

Neurons in the midbrain periaqueductal and periventricular gray matter excite neurons in the raphe nuclei of the brainstem that produce serotonin. Serotonergic fibers descend in the dorsolateral funiculus to activate enkephalin containing interneurons in the substantia gelatinosa. These cells appear to presynaptically inhibit incoming substance P - containing pain fibers, thereby reducing the central transmission of pain. The endogenous opiates (such as enkephalin) conceivably occupy the same receptors on pain fibers as morphine, accounting for the analgesic affects of enkephalin.

D. Treatment of Pain

a. Neurosurgical procedures, such as sectioning dorsal roots (rhizotomy); transection of the spinothalamic tract in the spinal cord (cordotomy).

b. Electrical stimulation of the skin by electrodes overlying the spinal cord or implanted against the dorsal columns. This presumably stimulates large diameter fibers that impede the flow of pain information centrally.

c. Electrical stimulation of the midbrain periaqueductal gray. This presumably releases enkephalin or other endogenous opiates in the dorsal horn that reduce the transmission of pain impulses.

d. Aspirin-like drugs that inhibit the synthesis of protaglandins thereby reducing the sensitivity of nociceptive receptors.