Rewiring Cortex: The Role of Patterned Activity in Development and Plasticity of Neocortical Circuits

Mriganka Sur, Alessandra Angelucci,* Jitendra Sharma

Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, E25-235, Cambridge, Massachusetts 02139

Received 10 May 1999; accepted 25 May 1999

ABSTRACT: Visually driven activity is not required for the establishment of ocular dominance columns, orientation columns, and long-range horizontal connections in visual cortex, although spontaneous activity appears to be necessary. The role of activity may be instructive or simply permissive; evidence for an instructive role requires inquiry into the role of the pattern of activity in shaping cortical circuits. The few experiments that have probed the role of patterned activity include the effects of artificial strabismus, artificial stimulation of the optic nerve, and rewiring visual projections from the retina to the auditory thalamus and cortex. These experiments demonstrate that patterned activity is vital for the maintenance of thalamocortical, local intracortical, and long-range horizontal connections in cortex. © 1999 John Wiley & Sons, Inc. J Neurobiol 41: 33–43, 1999

Keywords: **patterned activity; local circuits; long-range connections; rewired; ferret**

The precision of information processing in the adult neocortex relies on specific connections between neurons established during development. The developmental specification of neocortex involves the positioning of neurons within cortical laminae and the formation of distinct cortical areas, along with appropriate wiring of inputs into, outputs from, and connections within an area (Sur et al., 1990). While laminar and areal identity are determined by early events, mainly guided by molecular cues intrinsic to the brain (Goodman and Shatz, 1993), the wiring of connections between neurons is a protracted event that involves a combination of intrinsic and extrinsic determinants (Katz and Shatz, 1996). A great deal of work in the primary visual cortex (V1) has clarified the role of electrical activity as a key extrinsic factor in shaping neuronal connections during development. The purpose of this review is to examine the role of visually driven and of spontaneous activity in shaping connections in visual cortex. Alongside, we shall examine recent evidence defining the role of the pattern of activity, as distinguished from the amount of activity, in cortical development, placing in context experiments that involve the routing of visual projections to the auditory cortex of the brain as a specific paradigm for examining the role of patterned activity in the development of cortical processing circuits.

VISUAL EXPERIENCE, SPONTANEOUS ACTIVITY, AND THE DEVELOPMENT OF CORTICAL MODULES

A fundamental feature of the adult mammalian neocortex is its modular architecture. Some of the best studied examples of connectional and functional modules are the systems of ocular dominance and orientation columns in V1 of higher mammals. In carnivores and primates, thalamic afferents from the two

* *Present address:* Department of Visual Science, Institute of Ophthalmology, University College London, 11-43 Bath St., London EC1V 9EL, United Kingdom

Correspondence to: M. Sur

Contract grant sponsor: NIH; contract grant numbers: EY 07023, EY 11512

 CCC 0022-3034/99/010033-11

eyes segregate in layer 4 of V1 into a series of alternating eye-specific stripes, the ocular dominance bands (Hubel and Wiesel, 1969; Shatz et al., 1977), that represent the anatomical correlate of physiologically identified ocular dominance columns (Hubel and Wiesel 1962, 1968). In addition, most V1 cells respond best to an edge of a specific orientation at a particular location in the visual field. Neurons preferring the same orientation are grouped together in columns and represented adjacent to columns of neurons preferring adjacent orientations. Thus, there is a systematic map of orientation preference across V1 (Bonhoeffer and Grinvald, 1991, 1993; Blasdel, 1992; Rao et al., 1997). Within the upper layers of V1, reciprocal long-range horizontal connections, arising primarily from pyramidal neurons, preferentially link cortical columns sharing similar orientation preference, thus forming periodic patches of terminals (Gilbert and Wiesel, 1983, 1989; Rockland and Lund, 1983; Malach et al., 1993).

Several lines of evidence indicate that visual experience is required for the maintenance of ocular dominance columns, orientation columns, and the system of patchy long-range horizontal connections in V1, but is not required for their initial establishment. In primates, segregation of ocular dominance columns begins prenatally, but suturing an eyelid postnatally causes the columns of the deprived eye to shrink (Rakic, 1977). In cats and ferrets, ocular dominance segregation begins after the onset of visual experience (LeVay et al., 1978; Ruthazer et al., 1999), and monocular lid suture causes shrinkage of deprived eye columns (Shatz and Stryker, 1978; Antonini and Stryker, 1993), so that most V1 neurons are driven physiologically by the open eye (Wiesel and Hubel, 1963). Binocular manipulations such as binocular lid suture or dark rearing, on the other hand, do not alter the normal physiological ocular dominance distribution (Wiesel and Hubel, 1965; Fregnac and Imbert, 1978; Mower et al., 1981) and reduce but do not abolish the anatomical segregation of thalamocortical axons in layer 4 of V1 (Swindale, 1988).

Orientation selectivity is present in V1 of monkeys at birth (Wiesel and Hubel, 1974) and in a subset of V1 neurons in cats and ferrets at or before the time of natural eye opening, with the proportion of neurons gradually increasing after the onset of visual experience (Imbert and Buisseret, 1975; Blakemore and Van Sluyters, 1975; Fregnac and Imbert, 1978; Albus and Wolf, 1984; Chapman and Stryker, 1993). The time course of orientation map development parallels for the most part the development of orientation selectivity in single cells. Chronic optical imaging of intrinsic signals at different developmental ages in the same animal reveals that compared to adult maps, early maps show lower signal strength and broader orientation tuning, but orientation domains show similar size, location, orientation preference, and periodicity as in the adult (Chapman et al., 1996; Godecke et al., 1997; Crair et al., 1998). Short-term binocular deprivation impairs but does not entirely prevent maturation of orientation selective reponses (Pettigrew, 1974; Fregnac and Imbert, 1984; Chapman and Stryker, 1993), whereas prolonged deprivation leads to a progressive deterioration of specific receptive field properties (Fregnac and Imbert, 1978; Imbert and Buisseret, 1975; Mower et al., 1981). Short-term binocular suture also does not alter the normal layout of orientation maps as revealed by optical imaging of intrinsic signals (Crair et al., 1998; Godecke et al., 1997); however, long-term binocular suture induces a progressive deterioration of the orientation map (Crair et al., 1998). In cat area 18, 1 week of monocular lid suture after orientation maps have already formed disrupts the map from the closed eye; reverse lid suture restores the map precisely (Kim and Bonhoeffer, 1994). In addition, matching orientation maps for the two eyes develop even in cats raised under a reverse-suture paradigm from before the time of natural time opening, so that the two eyes never had common visual experience (Godecke and Bonhoeffer, 1996). Overall, these studies indicate that although visual experience is required for orientation selectivity and maps to reach full maturation and be maintained, the initial emergence of orientation selective responses in single cells and the overall layout of the orientation map are determined by visual experience-independent mechanisms.

In carnivores and primates, similar to the development of geniculocortical projections, the adult pattern of clustered horizontal connections in V1 emerges gradually from an initially diffuse pattern, passing through an intermediate stage of crudely organized clusters (Callaway and Katz, 1990; Galuske and Singer 1996; Durack and Katz, 1996; Ruthazer and Stryker, 1996; Coogan and van Essen, 1996). Whereas in primates adultlike clustered horizontal connections are fully in place prenatally, in cats and ferrets crude clusters first appear at or just before the time of natural eye opening, when only a subset of V1 cells shows orientation selective responses. Refinement of clusters occurs after the onset of vision, concomitant with the maturation of orientation selectivity and maps, and involves the selective elimination of misplaced long unbranched collaterals as well as the addition of new collaterals within clusters. Binocular deprivation prevents the refinement of clusters,

but not the initial emergence of crude clustering (Callaway and Katz, 1991).

While visual experience may not be necessary for the initial formation of thalamocortical and intracortical circuits, spontaneous neural activity may still be present and play a role in early development. Stryker and Harris (1986) demonstrated that silencing retinal activity by early, repeated, bilateral intraocular injections of tetrodotoxin (TTX), a sodium channel blocker, prevents segregation of thalamocortical axons in layer 4. Neural activity before the onset of vision is present in the retina as rhythmic bursts of action potentials spontaneously generated by retinal ganglion cells (Galli and Maffei, 1988). Such activity is temporally correlated among neighboring cells (Maffei and Galli-Resta, 1990; Meister et al., 1991) and persists until just before the onset of visually driven activity (Wong et al., 1993). Indeed, spontaneous retinal activity can drive cells of the lateral geniculate nucleus (LGN) to fire periodic bursts of action potentials (Mooney et al., 1996). Spontaneous bursts of activity are also present in the developing cortex (Yuste et al., 1992). Thus, initial segregation of ocular dominance domains, as well as the formation of orientation columns and clustered horizontal connections, may be guided by spontaneous activity in thalamic afferents and in the cortex itself. Consistent with this view, local intracortical infusion of TTX in ferrets at an early developmental stage prevents clustering of horizontal connections (Ruthazer and Stryker, 1996) and freezes orientation selectivity at an early immature state (Chapman and Stryker, 1993).

PATTERNED ACTIVITY AND THE FORMATION OF CORTICAL CIRCUITS

While neural activity, first spontaneously generated and later visually driven, likely plays a role in the establishment and maintenance of cortical circuits, it remains unclear whether the role is instructive or simply permissive. Specifically, does the spatial and temporal pattern of activity direct the formation of connections, or is simply the presence of activity above some threshold sufficient to trigger a developmental program that makes connections? Temporally correlated pre- and postsynaptic activity in the developmental rearrangement of cortical connections requires a hypothesis such as a Hebbian rule to govern the process, whereby synaptic connections are strengthened and stabilized when pre- and postsynaptic neurons are coactive, and weakened or eliminated when they are not (Hebb, 1949; Stent, 1973).

So far, only a few studies have examined the role of temporal patterning, rather than the overall level, of activity in cortical development. Strabismus is a condition of misalignment of the two eyes in which the images on the two retinae cannot be brought into register so that corresponding retinal loci in the two eyes are no longer temporally correlated, but the total amount of activity reaching the cortex through each eye is equal and similar to that in normal animals. Artificially induced strabismus causes neurons in V1 to become almost exclusively monocular (Hubel and Wiesel, 1965; Van Sluyters and Levitt, 1980) and ocular dominance bands to become sharper (Shatz et al., 1977) and wider than normal (Lowel, 1994; but see Jones et al., 1996), a result that conforms to theoretical predictions of a model based on strength of correlations (Goodhill, 1993; Goodhill and Lowel, 1995). These results indicate that the relative timing of activity is used at the cortical level to produce eye-specific segregation (or binocularity) when the two eyes are activated asynchronously (or synchronously). Correlated neural activity in corresponding retinal loci in the two eyes, however, is not necessary to establish the layout of orientation maps: Matching orientation maps develop when the two eyes have never had common visual experience (Godecke and Bonhoeffer, 1996; see above), and orientation maps are continuous across ocular dominance columns in strabismic cats (Lowel et al., 1994). Spontaneous retinal activity is likely not involved in setting up matching orientation maps for the two eyes, since this would require it to be synchronized between the two retinae. However, if the activity of LGN cells from the two eyes is correlated to some extent, but less than activity from the same eye, matching orientation maps can develop along with ocular dominance columns (Erwin and Miller, 1998). A correlation-based mechanism similar to that involved in ocular dominance development may drive the formation of horizontal connections. Whereas in normal cats clusters of horizontal connections do not align with ocular dominance columns, in strabismic cats intrinsic V1 connections link columns with similar eye dominance (Lowel and Singer, 1992) and orientation preference (Schmidt et al., 1997).

Asynchronous artificial stimulation of the two optic nerves in kittens after bilateral blockade of retinal activity with TTX causes V1 cells to become predominantly monocular, whereas synchronous activation creates predominantly binocular cells (Stryker and Strickland, 1984). Temporal activity patterns also play a crucial role in the development of orientation and direction selectivity in V1. In ferrets, perturbing the normal patterns of spontaneous afferent activity by artificially stimulating an optic nerve just before

eye opening, when orientation selective responses are present only in a small percentage of cells and before orientation maps first emerge, perturbs the development of orientation and direction selectivity in V1 but does not alter the overall layout of orientation maps (Weliky and Katz, 1997). Interestingly, orientation- and direction-selective responses are not entirely abolished by this manipulation, perhaps because artificial stimulation was initiated after some orientation selectivity has already formed. In addition, because the distribution of selective responses in V1 of the stimulated animals resembles that of normal immature ferrets, these results are consistent with both the aberrant activity patterns having altered the development of receptive fields and with having simply arrested their development in the initial immature state.

CROSS-MODAL PLASTICITY AS A PARADIGM FOR STUDYING THE ROLE OF PATTERNED ACTIVITY

A different paradigm for examining the role of the pattern of afferent activity in the development of cortical circuits involves routing retinal projections to the auditory pathway in ferrets (Sur et al., 1988). Retinal axons in mammals normally project to the LGN and the superior colliculus [Fig. 1(A)], while auditory afferents from the inferior colliculus normally project to the medial geniculate nucleus (MGN). Deafferenting the MGN in neonatal ferrets by extensively sectioning its ascending auditory inputs (Angelucci et al., 1998) causes retinal projections to innervate the MGN [Fig. 1(B)]. These inputs provide a pathway for visual driving of the auditory cortex; importantly, the axons that project from the MGN to primary auditory cortex (A1) and other auditory cortical areas remain the same, but now are driven by retinal/visual rather than by auditory activity. Hence, auditory cortex in rewired ferrets develops with a very different pattern of input activity from normal.

The retinal ganglion cells that project to the MGN include cells with small somata and fine axons—these features are characteristic of the population of W cells in the retina (Roe et al., 1993; Pallas et al., 1994a)—although the caliber of retino-MGN axons can extend up to the largest diameter axons in the optic tract (Angelucci et al., 1998). Thus, most if not all retinal ganglion cell types can direct their axons to the MGN. The factors that induce retinal axons to project into a deafferented MGN are under active study and may include regulation of membrane-bound molecules (Lyckman et al., 1999) or diffusible factors.

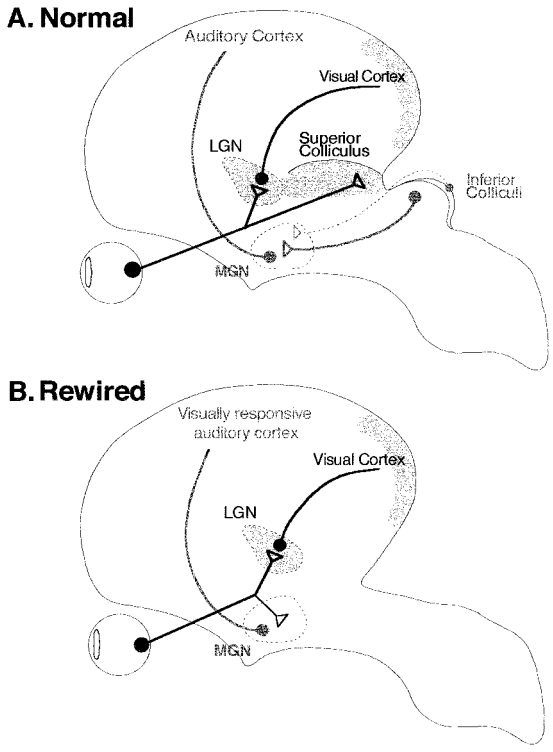

Figure 1 Visual and auditory pathways in normal ferrets, and the pathway from the retina to auditory cortex in rewired ferrets. (A) In normal animals, the visual pathway (black lines) starts with projections from the retina to the lateral geniculate nucleus (LGN) and to the superior colliculus. The LGN projects to the visual cortex. In the auditory pathway (gray lines), the major subcortical input to the medial geniculate nucleus (MGN) is the ipsilateral inferior colliculus; smaller inputs (dashed line) arise from the contralateral inferior colliculus. The MGN projects to the auditory cortex. (B) In rewired animals, projections from the retina can be routed to the MGN by extensive neonatal deafferentation of the MGN (by sectioning the major inputs to the MGN). The projection from the MGN to auditory cortex is unaltered, and retinal inputs thus activate the MGN and auditory cortex. Adapted from Angelucci et al. (1998).

Retinal projections to the MGN provide a unique way to examine the relative roles of afferents and targets in forming patterns of termination and contact. In normal ferrets, retinal axons within the LGN are segregated into eye-specific layers and further into sublayers that receive inputs from on-center and off-center retinal ganglion cells (Roe et al., 1989). In contrast, axons from the inferior colliculus normally segregate within the ventral division of the MGN into thin lamellae that each represent a narrow range of sound frequencies. Retinal projections to the MGN are initially diffuse and the projections from the two eyes overlap extensively. These projections segregate in the first 3 weeks to form eye-specific clusters

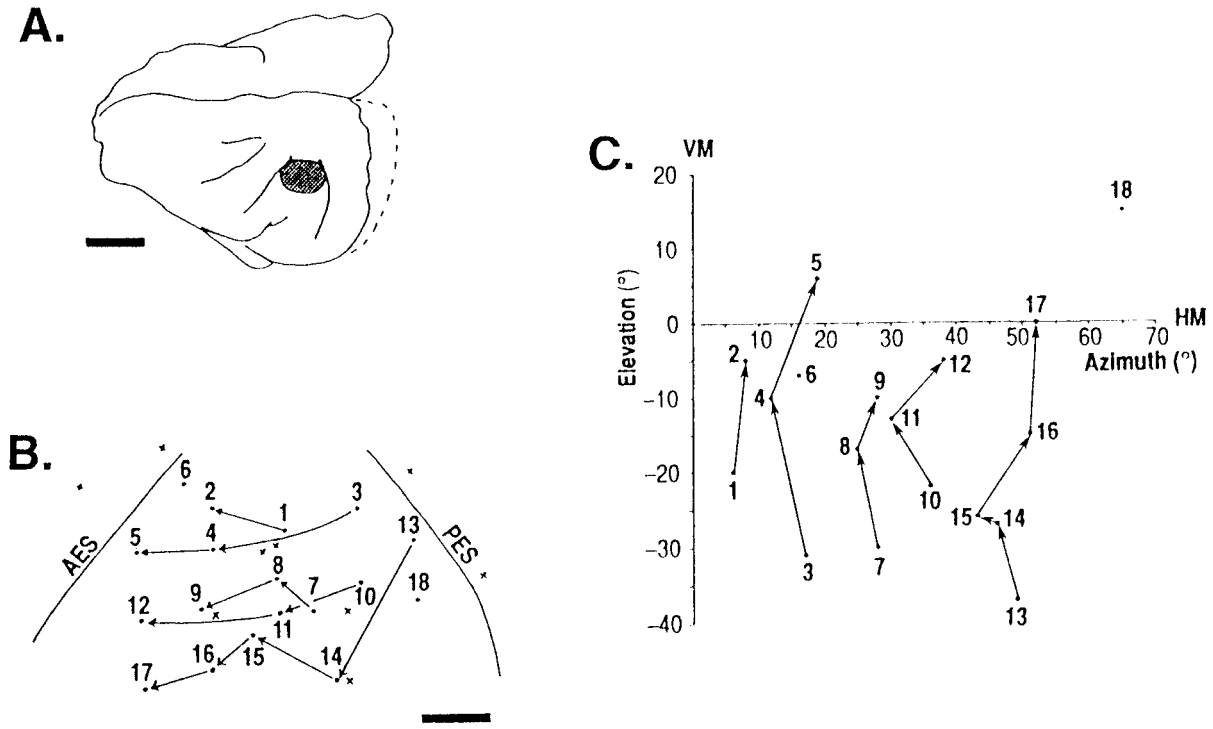

Figure 2 Map of visual space within primary auditory cortex in a rewired ferret. (A) Dorsolateral view of the brain in which the visual field representation was mapped in rewired A1 (shown as stippled region on the brain). The dotted line at the back of the brain represents a portion of visual cortex that was ablated neonatally in this animal as part of an earlier protocol to induce retinal projections into the MGN. This lesion was not made in a later protocol (see Fig. 1), and it has no effect on the rewiring or on the visual responses recorded from A1. Scale bar = 5 mm. (B) Expanded view of the recording sites within rewired A1. Sites marked by an "x" denote locations at which no visual receptive field could be mapped. AES = anterior ectosylvian sulcus; PES = posterior ectosylvian sulcus. Scale bar = 1 mm. (C) Progressions of receptive field centers corresponding to rows of recording sites shown in (B). The receptive fields themselves are not drawn; receptive field centers ranged from 4° to 20°. VM = vertical meridian; HM = horizontal meridian. Adapted from Roe et al. (1990).

whose shape, size, and orientation match those of relay cell dendrites within the MGN lamellae (Angelucci et al., 1997). The progressive remodeling of retinal axon arbors within the MGN into small but distinct eye-specific regions indicates that differences in the pattern of activity between the two eyes are instrumental in this segregation. However, the eye-specific clusters form patches aligned with the intrinsic lamellar organization of the MGN rather than continuous eye-specific layers or on/off sublayers as in the LGN, indicating that the target regulates the overall organization of the afferent projection pattern.

The visual response properties of MGN cells in rewired animals resemble their retinal ganglion cell input. Importantly, MGN cells have either on-center or off-center receptive fields that do not exhibit any significant tuning for orientation or direction (Roe et al., 1993). There is also a topographic mapping of retinal input in the MGN (Roe et al., 1991) shaped by focal terminal arbors of retinal ganglion cell axons in appropriate regions of the nucleus (Pallas et al., 1994b).

In rewired A1, the topographic mapping of visual space, the orientation-selective response properties of neurons, and the map of orientation-selective cells all provide clues to the interaction between afferent activity and target substrates in shaping cortical circuits. The map of visual space in rewired cortex (Roe et al., 1990) is illustrated in Figure 2, which shows a grid of electrode penetrations in the cortex [Fig. 2(B)] and the location of corresponding receptive field centers in the visual field [Fig. 2(C)]. Visual field azimuth is mapped with receptive fields near the vertical midline represented medially in cortex and peripheral fields represented laterally. Elevation is mapped in Figure 2 with lower visual fields represented posteriorly in

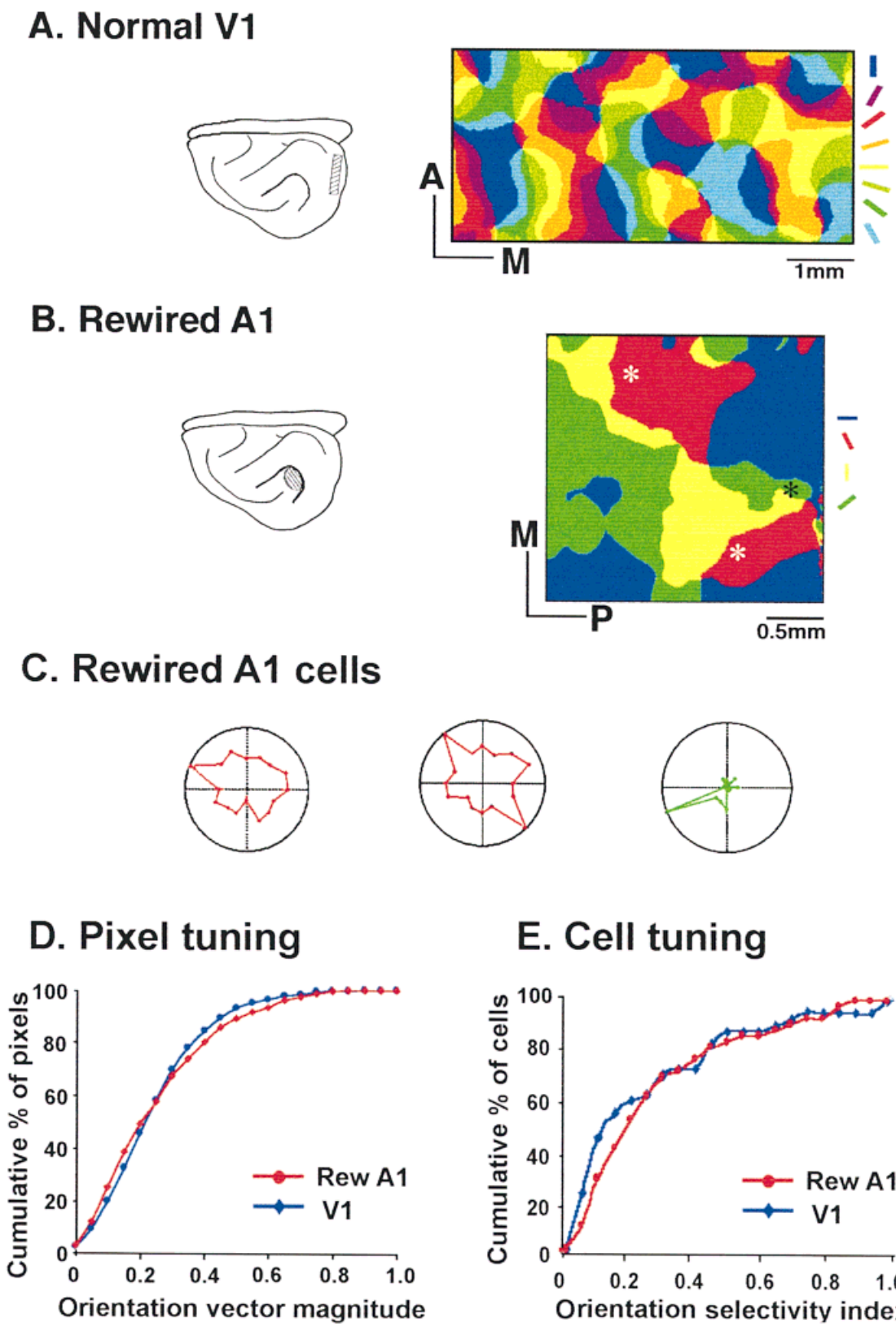
A. Normal V1
A
M
1mm
B. Rewired A1
M
P
0.5mm
C. Rewired A1 cells
D. Pixel tuning
Cumulative % of pixels
100
80
60
40
20
0
0
0.2
0.4
0.6
0.8
1.0
Orientation vector magnitude
Rew A1
V1
E. Cell tuning
Cumulative % of cells
Orientation selectivity index
Rew A1
V1

Figure 3

cortex and upper fields represented anteriorly. In normal ferrets, primary auditory cortex maps the cochlea with low sound frequencies represented laterally and high sound frequencies medially in cortex (Kelly et al., 1986); the anteroposterior axis maps the same sound frequency and represents an isofrequency axis. Since rewired A1 is now shown to represent a two-dimensional sensory surface (the retina) topographically, the form of a map is not an intrinsic property of the cortex. Nonetheless, both direct and indirect evidence indicates that the map in rewired cortex arises not by a fundamental change in the structure of projections, but by an activity-dependent process. Anatomically, projections from the MGN to A1 are normally extensively overlapped along the isofrequency dimension, consistent with thalamocortical arbors that are narrow along the variable frequency axis but elongated along the isofrequency axis (Andersen et al., 1980). Such projections are not altered in rewired ferrets; i.e., thalamocortical axons still spread extensively along the anteroposterior dimension of cortex (Angelucci, 1996; Pallas et al., 1990). These convergent-and-divergent projections would not normally allow a topographic representation. Thus, visual topography in the cortical map along this dimension is likely created within the cortex, by activity-dependent selection and strengthening of the appropriate subset of inputs during development from the potentially extensive set available anatomically. Consistent with this idea, the representation of elevation in rewired cortex (along the anteroposterior axis) is less precise than the representation of azimuth, and can even reverse in polarity in some animals (Roe et al., 1990).

Nearly all of the response features of single neurons in rewired cortex are comparable to those in normal V1 (Roe et al., 1992). Thus, rewired cells show selectivity for orientation, direction, and velocity, with selectivity indices that are statistically indistinguishable from those in V1. Rewired cortex has similar proportions of simple and complex cells as normal V1. Figure 3 shows the orientation map of normal V1 and rewired A1 from a typical animal each (Sharma et al., 1996), polar tuning plots of rewired A1 cells, and a comparison of the orientation tuning of individual pixels in the orientation maps and of single cells recorded in the cortex. The magnitude of the orientation vector of single pixels (a measure of tuning strength derived from the optically imaged response to a range of stimulus orientations) is similar between rewired A1 and normal V1 [Fig. 3(D) shows the mean cumulative distributions derived from rewired and normal animals.] The cumulative distribu-

Figure 3 Orientation tuning and orientation maps in primary visual cortex of normal ferrets and in primary auditory cortex of rewired ferrets. (A) The orientation map in V1: optical imaging of intrinsic signals reveals a systematic map of orientation selective domains. The map of orientation angle is obtained by computing a vector average at each pixel of the responses to drifting gratings of eight different orientations. The orientation at each pixel is coded according to the color key at right. The orientation map shows domains representing different orientations arrayed in pinwheel fashion around singularities (at pinwheel centers). Each orientation is represented in a regular, quasi-periodic lattice on cortex. A = anterior; M = medial. (B) The orientation map in rewired A1, obtained in similar fashion as the V1 map but with stimuli of four different orientations. The orientation at each pixel is coded according to the key at right. The orientation map shows a few pinwheel centers around which the different orientation domains are arrayed. The density of pinwheel centers is less than in V1, as is the regularity of their spacing. Orientation domains are larger on average than those in V1, and are also represented less periodically on cortex. Stars denote location of cells recorded in the same animal that are shown in (C). M = medial; P = posterior. (C) Polar tuning plots of representative cells recorded in the same rewired animal. Plots in red denote cells recorded at sites in the red domains of the orientation map in (B) (white stars); the plot in green shows a cell recorded in a green domain [black star in (B)]. These plots show the total spikes in response to gratings of eight different orientations drifting in orthogonal directions. The optimal orientation of each cell is reasonably matched to the optically imaged orientation domain in which it is located. (D) Cumulative distributions of the magnitude of the orientation vector of pixels in V1 and rewired A1 maps. The orientation vector magnitude represents the strength of orientation tuning in cortex: low magnitudes are due to either broad tuning or weak responses, while high magnitudes imply sharp tuning and strong responses. The data are averages from three normal V1 animals and four rewired A1 animals. The orientation tuning of pixels is very similar in V1 and rewired A1. (E) Cumulative distributions of the orientation selectivity index of cells in V1 and rewired A1. The orientation selectivity index was calculated in the same manner as the pixel orientation vector, by vector averaging the response to eight different orientations. The orientation selectivity index of cells is very similar in V1 and rewired A1.

tion of the orientation selectivity index of cells in rewired A1 and normal V1 [Fig. 3(E)] also indicates that the two areas have very similarly tuned cells. Just as in V1, the orientation tuning of rewired A1 cells arises in the cortex itself, for MGN cells are not orientation selective (Roe et al., 1993). Thus, the same mechanisms that lead to orientation tuning in V1 are likely to operate in rewired cortex. A reasonable possibility is that the tuning arises by small orientation biases in thalamocortical inputs that are amplified by recurrent excitatory networks in cortex (Somers et al., 1995; Ben-Yishai et al., 1995; Douglas et al., 1995). These recurrent connections are possibly an ubiquitous feature of cortex, but they could also be shaped by the pattern of afferent/visual activity that drives V1 and rewired A1 during development.

In contrast to the similarity in orientation tuning of single cells and pixels, the map of orientation selective cells in rewired A1 is quite different from that in normal V1 (Fig. 3). V1 has a regular, spatially periodic spacing of similar-sized iso-orientation domains that respond to any particular stimulus orientation (Rao et al., 1997), and these domains contribute to a periodic representation of orientations and of pinwheel centers or orientation singularities in the cortex [Fig. 3(A)]. Rewired A1, on the other hand, has larger iso-orientation domains that are also organized much less periodically in the cortex [Fig. 3(B)]. The difference in domain periodicity is evident in the autocorrelation and power spectra of the orientation maps that can be computed from the raw images. Since the layout of orientation domains reflects the long-range horizontal connections between superficial layer neurons, we have analyzed these connections in V1 and rewired A1, as well as normal A1. Long-range connections are highly patchy and periodic in V1, while they extend along the isofrequency axis rather homogeneously in normal A1. In rewired A1, the connections are more patchy and periodic than in normal A1 but less so than in V1, in a manner that reflects the differences between the orientation maps (J. Sharma, A. Angelucci, and M. Sur, submitted). Thus, visual input reorganizes horizontal connections but to an extent that is constrained by the intrinsic features of the cortex.

These experiments reveal the interplay between afferent and target, and between activity-dependent and intrinsic determinants, in the development of neural circuits and connections. Subcortically, activity is involved in eye-specific segregation in the retino-MGN projection, but its role is circumscribed by the lamellar organization of the MGN. The chronological development of orientation tuning or of the orientation map has not been examined in rewired cortex, but it is parsimonious to assume that these would be present at least in crude form at an early stage, similar to V1. Along with other experiments, the findings in rewired A1 demonstrate that patterned activity has a role in at least maintaining thalamocortical, local intracortical, and long-range horizontal circuits. Axons that project from the MGN to A1 do not show obvious changes in their morphology and arbor extent after rewiring, but the effectiveness of their synapses in creating a topographic map is shaped importantly by the pattern of activity that drives them. Rewiring and artificial stimulation of the optic nerve are seen to have complementary effects on cortical responses: Whereas artificial stimulation degrades orientation tuning but leaves the orientation map unaltered (Weliky and Katz, 1997), rewiring leads to orientation tuning in rewired A1 that is highly comparable to V1 but an orientation map that is less organized. Together, these data demonstrate that the orientation tuning of cells is separable from their organization into an orientation map. Furthermore, the two kinds of experiment argue that the thalamocortical and local intracortical connections that generate orientation tuning are influenced by patterned activity. The orientation map reflects the nature of long-range horizontal connections: These are very different between V1 and A1 and underlie the differences in domain size and periodicity between V1 and rewired A1. The long-range connections too are not a static feature of cortex—they are altered in strabismic cats (Lowel and Singer, 1992; Schmidt et al., 1997), and they are shaped in rewired A1 so as to somewhat resemble connections in V1. Finally, the corticocortical connections of rewired cortex appear not to be different from normal A1 (Pallas et al., 1993), although more subtle changes in cortical projections that might underlie the ability of rewired cortex to mediate visual behavior (Carman et al., 1992) cannot be ruled out.

The authors thank Courtney Hunter-Melo for assistance in preparing the manuscript. This study was supported by NIH Grants EY 07023 and EY 11512.

REFERENCES

Albus K, Wolf K. 1984. Early postnatal development of neuronal function in the kitten's visual cortex: a laminar analysis. J Physiol Lond 348153–185.

Andersen RA, Knight PL, Merzenich MM. 1980. The thalamocortical and corticothalamic connections of AI, AII, and the anterior auditory field (AAF) in the cat: evidence for two largely segregated systems of connections. J Comp Neurol 194:663–701.

Angelucci A. 1996. Experimental retinal projections to the ferret auditory thalamus: morphology, development and effects on auditory cortical organization. Ph.D. thesis, Massachusetts Institute of Technology.

Angelucci A, Clascá F, Bricolo E, Cramer KS, Sur M. 1997. Experimentally induced retinal projections to the ferret auditory thalamus: development of clustered eye-specific patterns in a novel target. J Neurosci 17:2040–2055.

Angelucci A, Clascá F, Sur M. 1998. Brainstem inputs to the ferret medial geniculate nucleus and the effect of early deafferentation on novel retinal projections to the auditory thalamus. J Comp Neurol 400:417–439.

Antonini A, Stryker MP. 1993. Rapid remodeling of axonal arbors in the visual cortex. Science 260:1819–1821.

Ben-Yishai R, Lev Bar-Or R, Sompolinsky H. 1995. Orientation tuning by recurrent neural networks in visual cortex. Proc Natl Acad Sci USA 92:3844–3848.

Blakemore C, Van Sluyters RC. 1975. Innate and environmental factors in the development of the kitten's visual cortex. J Physiol Lond 248:663–716.

Blasdel GG. 1992. Orientation selectivity, preference, and continuity in monkey striate cortex. J Neurosci 12:3139–3161.

Bonhoeffer T, Grinvald A. 1991. Orientation columns in cat are organized in pinwheel like patterns. Nature 353:429–431.

Bonhoeffer T, Grinvald A. 1993. The layout of iso-orientation domains in area 18 of cat visual cortex: optical imaging reveals pin-wheel like organisation. J Neurosci 13:4157–4180.

Callaway EM, Katz LC. 1990. Emergence and refinement of clustered horizontal connections in cat striate cortex. J Neurosci 10:1134–1154.

Callaway EM, Katz LC. 1991. Effects of binocular deprivation in the development of clustered horizontal connections in cat striate cortex. Proc Natl Acad Sci USA 88:745–749.

Carman L, Pallas SL, Sur M. 1992. Visual inputs routed to the auditory pathway in ferrets: behavioral results. Soc Neurosci Abstr 18:592.

Chapman B, Stryker MP. 1993. Development of orientation selectivity in ferret visual cortex and effects of deprivation. J Neurosci 13:5251–5262.

Chapman B, Stryker MP, Bonhoeffer T. 1996. Development of orientation preference maps in ferret primary visual cortex. J Neurosci 16:6443–6453.

Coogan TA, Van Essen DC. 1996. Development of connections within and between areas V1 and V2 of macaque monkeys. J Comp Neurol 372:327–342.

Crair MC, Gillespie DC, Stryker MP. 1998. The role of visual experience in the development of columns in cat visual cortex. Science 279:566–570.

Douglas RJ, Koch C, Mahowald M, Martin KAC, Suarez HH. 1995. Recurrent excitation in neocortical circuits. Science 269:981–985.

Durack JC, Katz LC. 1996. Development of horizontal projections in layer 2/3 of ferret visual cortex. Cereb Cortex 6:178–183.

Erwin E, Miller KD. 1998. Correlation-based development of ocularly matched orientation and ocular dominance maps: determination of required input activities. J Neurosci 18:9870–9895.

Frégnac Y, Imbert M. 1978. Early development of visual cortical cells in normal and dark-reared kittens: relationship between orientation selectivity and ocular dominance. J Physiol Lond 278:27–44.

Frégnac Y, Imbert M. 1984. Development of neuronal selectivity in primary visual cortex of cat. Physiol Rev 64:325–434.

Galli L, Maffei L. 1988. Spontaneous impulse activity of rat retinal ganglion cells in prenatal life. Science 242:90–91.

Galuske RAW, Singer W. 1996. The origin and topography of long-range intrinsic projections in cat visual cortex: a developmental study. Cereb Cortex 6:417–430.

Gilbert CD, Wiesel TN. 1983. Clustered intrinsic connections in cat visual cortex. J Neurosci 3:1116–1133.

Gilbert CD, Wiesel TN. 1989. Columnar specificity of intrinsic horizontal and corticocortical connections in cat visual cortex. J Neurosci 9:2432–2442.

Gödecke I, Bonhoeffer T. 1996. Development of identical orientation maps for the two eyes without common visual experience. Nature 379:251–254.

Gödecke I, Kim D-S, Bonhoeffer T, Singer W. 1997. Development of orientation preference maps in area 18 of kitten visual cortex. Eur J Neurosci 9:1754–1762.

Goodhill GJ. 1993. Topography and ocular dominance: a model exploring positive correlations. Biol Cybern 69: 109–118.

Goodhill GJ, Löwel S. 1995. Theory meets experiment: correlated neural activity helps determine ocular dominance column periodicity. Trends Neurosci 18:437–439.

Goodman CS, Shatz CJ. 1993. Developmental mechanisms that generate precise patterns of neuronal connectivity. Cell 10:77–98.

Hebb DO. 1949. The organization of behavior. New York: Wiley. p. 1–335.

Hubel DH, Wiesel TN. 1962. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 160:106–154.

Hubel DH, Wiesel TN. 1965. Binocular interaction in striate cortex of kittens reared with artificial squint. J Neurophysiol 28:1041–1059.

Hubel DH, Wiesel TN. 1968. Receptive fields and functional architecture of monkey striate cortex. J Physiol Lond 195:215–243.

Hubel DH, Wiesel TN. 1969. Anatomical demonstration of columns in the monkey striate cortex. Nature 221:747–750.

Imbert M, Buisseret P. 1975. Receptive field characteristics and plastic properties of visual cortical cells in kittens reared with or without visual experience. Exp Brain Res 22:25–36.

Jones DG, Murphy KM, Van Sluyters RC. 1996. Spacing of ocular dominance columns is not changed by monocular deprivation or strabismus. Invest Opthalmol Vis Sci 37: 1964.

Katz LC, Shatz CJ. 1996. Synaptic activity and the construction of cortical circuits. Science 274:1133–1138.

Kelly JB, Judge PW, Phillips DP. 1986. Representation of the cochlea in primary auditory cortex of the ferret (*Mustela putorius*). Hearing Res 24:111–115.

Kim D-S, Bonhoeffer T. 1994. Reverse occlusion leads to a precise restoration of orientation preference maps in visual cortex. Nature 370:370–372.

Le Vay S, Stryker MP, Shatz CJ. 1978. Ocular dominance columns and their development in layer IV of the cat's visual cortex: a quantitative study. J Comp Neurol 179: 223–244.

Löwel S. 1994. Ocular dominance column development: strabismus changes the spacing of adjacent columns in cat visual cortex. J Neurosci 14:7451–7468.

Löwel S, Singer W. 1992. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. Science 255:209–255.

Löwel S, Schmidt KE, Kim D-S, Singer W, Bonhoeffer T. 1994. Continuity of iso-orientation domains across ocular dominance borders in area 17 of strabismic cats. Eur J Neurosci 7:77.

Lyckman AW, Jhaveri S, Feldheim D, Frisén J, Flanagan JG, Sur M. 1999. Do ephrin-A and EphA serve in compartmentalization of visual and auditory structures in developing thalamus? Soc Neurosci Abstr (in press).

Maffei L, Galli-Resta L. 1990. Correlation in the discharges of neighboring rat retinal ganglion cells during prenatal life. Proc Natl Acad Sci USA 87:2861–2864.

Malach R, Amir Y, Harel M, Grinvald A. 1993. Relationship between intrinsic connections and functional architecture revealed by optical imaging and *in vivo* targeted biocytin injections in primate striate cortex. Proc Natl Acad Sci USA 90:10469–10473.

Meister M, Wong ROL, Baylor DA, Shatz CJ. 1991. Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. Science 252:939–943.

Mooney R, Penn AA, Gallego R, Shatz CJ. 1996. Thalamic relay of spontaneous retinal activity prior to vision. Neuron 17:863–874.

Mower GD, Caplan CJ, Christen WG, Duffy FH. 1985. Dark rearing prolongs physiological but not anatomical plasticity of the cat visual cortex. J Comp Neurol 235: 448–466.

Pallas SL, Hahm J-O, Sur M. 1994a. Morphology of axons induced to arborize in a novel target, the medial geniculate nucleus. I. Comparison with arbors in normal targets. J Comp Neurol 347:1–20.

Pallas SL, Roe AW, Sur M. 1990. Visual projections induced into the auditory pathway of ferrets: I. Novel inputs to primary auditory cortex (AI) from the LP/pulvinar complex and the topography of the MGN-AI projection. J Comp Neurol 298:50–68.

Pallas SL, Sur M. 1993. Visual projections induced into the auditory pathway of ferrets. II. Corticocortical connections of primary auditory cortex. J Comp Neurol 336: 317–333.

Pallas SL, Sur M. 1994b. Morphology of axons induced to arborize in a novel target, the medial geniculate nucleus. II. Comparison with arbors from the inferior colliculus. J Comp Neurol 347:21–35.

Pettigrew JD. 1974. The effect of visual experience on the development of stimulus specificity by kitten cortical neurons. J Physiol Lond 237:49–74.

Rakic P. 1977. Prenatal development of the visual system in rhesus monkey. Phil Trans R Soc Lond B 278:245–260.

Rao SC, Toth LJ, Sur M. 1997. Optically imaged maps of orientation preference in primary visual cortex of cats and ferrets. J Comp Neurol 387:358–370.

Rockland KS, Lund JS. 1983. Intrinsic laminar lattice connections in primate visual cortex. J Comp Neurol 216: 303–318.

Roe AW, Garraghty PE, Esguerra M, Sur M. 1993. Experimentally induced visual projections to the auditory thalamus in ferrets: evidence for a W cell pathway. J Comp Neurol 334:263–280.

Roe AW, Garraghty PE, Sur M. 1989. The terminal arbors of single on-center and off-center X and Y retinal ganglion cell axons within the ferret's lateral geniculate nucleus. J Comp Neurol 288:208–242.

Roe AW, Hahm J-O, Sur M. 1991. Experimentally induced establishment of visual topography in auditory thalamus. Soc Neurosci Abstr 17:898.

Roe AW, Pallas SL, Hahm J-O, Sur M. 1990. A map of visual space induced in primary auditory cortex. Science 250:818–820.

Roe AW, Pallas SL, Kwon YH, Sur M. 1992. Visual projections routed to the auditory pathway in ferrets: receptive fields of visual neurons in primary auditory cortex. J Neurosci 12:3651–3664.

Ruthazer ES, Baker GE, Stryker MP. 1999. Development and organization of ocular dominance bands in primary visual cortex of the sable ferret. J Comp Neurol 407:151–165.

Ruthazer ES, Stryker MP. 1996. The role of activity in the development of long-range horizontal connections in area 17 of the ferret. J Neurosci 16:7253–7269.

Schmidt KE, Kim D-S, Singer W, Bonhoeffer T, Löwel S. 1997. Functional specificity of long-range intrinsic and interhemispheric connections in the visual cortex of strabismic cats. J Neurosci 17:5480–5492.

Sharma J, Angelucci A, Rao SC, Sheth BR, Sur M. 1996. Auditory cortex with induced visual projections: horizontal connectivity and optical imaging of functional responses. Soc Neurosci Abstr 22:1730.

Shatz CJ, Lindstrom SH, Wiesel TN. 1977. The distribution of afferents representing the right and left eyes in the cat's visual cortex. Brain Res 131:103–116.

Shatz CJ, Stryker MP. 1978. Ocular dominance of layer IV of the cat's visual cortex and the effects of monocular deprivation. J Physiol Lond 218:267–283.

Somers DC, Nelson SB, Sur M. 1995. An emergent model of orientation selectivity in cat visual cortical simple cells. J Neurosci 15:5448–5465.

Stent GS. 1973. A physiological mechanism for Hebb's postulate of learning. Proc Natl Acad Sci USA 70:997–1001.

Stryker MP, Harris W. 1986. Binocular impulse blockade prevents the formation of ocular dominance columns in cat visual cortex. J Neurosci 6:2117–2133.

Stryker MP, Strickland SL. 1984. Physiological segregation of ocular dominance columns depends on the pattern of afferent electrical activity. Invest Opthalmol Vis Sci 25:278.

Sur M, Garraghty PE, Roe AW. 1988. Experimentally induced visual projections into auditory thalamus and cortex. Science 242:1437–1441.

Sur M, Pallas SL, Roe AW. 1990. Cross-modal plasticity in cortical development: differentiation and specification of sensory neocortex. Trends Neurosci 13:227–233.

Swindale NV. 1988. Role of visual experience in promoting segregation of eye dominance patches in the visual cortex of the cat. J Comp Neurol 267:472–488.

Van Sluyters RC, Levitt FB. 1980. Experimental strabismus in the kitten. J Neurophysiol 43:686–699.

Weliky M, Katz LC. 1997. Disruption of orientation tuning in visual cortex by artificially correlated neuronal activity. Nature 386:680–685.

Wiesel TN, Hubel DH. 1963. Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol 26:1003–1017.

Wiesel TN, Hubel DH. 1965. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. J Neurophysiol 28:1029–1040.

Wiesel TN, Hubel DH. 1974. Ordered arrangement of orientation columns in monkeys lacking visual experience. J Comp Neurol 158:307–318.

Wong ROL, Meister M, Shatz CJ. 1993. Transient period of correlated bursting activity during development of the mammalian retina. Neuron 11:923–938.

Yuste R, Peinado A, Katz LC. 1992. Neuronal domains in developing neocortex. Science 257:665–669.