Reorganization of Retinotopic Cortical Maps in Adult Mammals After Lesions of the Retina

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unusual level of biological regulation with multiple fates and hence multiple functions encoded within a single species of mRNA, and (iii) new variables and caveats to be considered in the prediction of protein structure from primary sequence.

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31. The SP6 expression plasmids were constructed as follows. Plasmid pSPHaPrP: PrP cDNA from Syrian hamster isolate was cloned into SP6 (*19*). Plasmid pSPVSV G: pRSVG was cut with Hind III and Bgl II, gel-purified and ligated with T4 DNA ligase into vector pSP64T (that had been opened with Hind III and Bgl II and treated with calf intestinal phosphatase). Plasmid pSPVSV Gxk: a Kpn I site and an Xba I site were introduced via site-directed mutagenesis at codons 72 and 114, respectively, or pSPHaPrP. The resultant plasmid was opened at the Xba I site, blunted with the Klenow fragment, and ligated to a Kpn I 8-base fragment with T4 DNA ligase. The plasmid was then cut with Kpn I, and the 126-bp fragment was gel-purified and religated into pSPVSV G vector opened at codon 346 with Kpn I to create an in-frame fusion.
32. To ensure translation was completely blocked, a mock control was done in parallel without transcript during the initial 30-min translation. The sample was then split and one portion was treated with ATA and emetine and the other with H_2O and compensating salts. Transcript was then added and reactions were allowed to incubate the remaining 40 min. The sample that was treated with protein synthesis inhibitors did not synthesize product, whereas the sample that received mock inhibitors did (*21*).
33. A decrease in the number of chains after proteolysis of posttranslational translocation reaction was reproducibly observed. This phenomenon is observed with other proteins translocated after translation (*21*).
34. We thank J. Rose for the VSV G cDNA and J. Forsayeth and members of the Lingappa lab for useful comments. Special thanks to C. Wilson and members of the departments of neurosurgery and neurology for help at a critical phase of this work. This work was supported by NIH grants AG02132 and NS14069 to V.R.L., R.M.M., and S.B.P.

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The organization of the visual cortex has been considered to be highly stable in adult mammals. However, 5° to 10° lesions of the retina in the contralateral eye markedly altered the systematic representations of the retina in primary and secondary visual cortex when matched inputs from the ipsilateral eye were also removed. Cortical neurons that normally have receptive fields in the lesioned region of the retina acquired new receptive fields in portions of the retina surrounding the lesions. The capacity for such changes may be important for normal adjustments of sensory systems to environmental contingencies and for recoveries from brain damage.

ARE THE MAPS OF VISUAL SPACE IN visual cortex capable of reorganization in adult mammals? As in other mammals, the visual cortex of cats contains several retinotopic representations of the visual field, including those in areas 17 and 18 (*1*). Such systematic representations of peripheral receptor arrays also characterize somatosensory and auditory cortex (*2*). Under normal circumstances, these sensory maps develop in a highly consistent manner in individuals of the same species. However, development of these topological maps can be altered by abnormal sensory inputs, including those produced by sensory deprivation and damage to the peripheral sensory sheet (*3, 4*). Thus, the nature of the input from the receptor sheet partly determines the ultimate organization of developing sensory maps. In the visual system, sensory manipulations such as monocular deprivation, induced strabismus, and unilateral defocusing of the image can alter cortical organization (*3*). However, these manipulations affect cortical organization mainly or only within a critical developmental period extending a few months postnatally in cats or several years in humans (*3*). Thus, evidence supports the view that the organization of visual cortex remains highly stable after initial development, and there has been little reason to suppose that basic features of retinotopic maps can change in adults.

In contrast to the visual system, recent experiments on somatosensory cortex indicate that the organization of sensory maps can be modified even in adults (*4, 5*). For example, if part of the normal representation of the hand in primary somatosensory cortex is deprived of its normal source of activation by cutting a peripheral nerve, the cortical representation reorganizes over a period of hours to weeks so that neurons in the deprived zone of cortex acquire new receptive fields on other parts of the hand. Such adult plasticity implies that previously existing connections in the brain are capable of changing in synaptic effectiveness so that new receptive fields and new representational organizations can emerge in cortex. Such changes could be important in normal adjustments of the brain to alterations in the sensory environment, as well as in compensations for peripheral and central damage to the nervous system. Because the potential for such reorganization would seem to exist in other sensory fields, we investigated the possibility of adult plasticity in visual cortex with an experimental approach that has been used successfully for the somatosensory system.

Parts of areas 17 and 18 of the visual cortex were deprived of a normal source of activation by placing lesions 5° to 10° in diameter just above the area centralis in the retina of one eye of adult cats (*6*). By itself this procedure produced no notable change in retinotopic organization when tested in one cat. Most cortical neurons are binocularly activated and thus have two retinotopi-

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cally matched receptive fields. Hence, recordings made after a retinal lesion simply demonstrated restricted regions of cortex where neurons had receptive fields only in the intact eye. The monocular lesion, therefore, merely revealed an effect of removing one of two sources of activation, rather than any basic reorganization (7). However, when restricted zones of cortex were totally deprived of normal sources of visual activation by placing a lesion in one eye and removing the other eye, dramatic changes in the retinotopic organization of areas 17 and 18 were produced. Neurons in the deprived zone of cortex acquired new receptive fields representing inputs from retinal locations around the margins of the lesion.

To allow time for cortical reorganization to occur, most of our recordings were made 2 to 6 months after the retinal lesion and the enucleation of the other eye. In each experiment, microelectrode recordings were made from neurons in an array of closely spaced electrode penetrations within and around the deprived cortex (*8*). Outside the zone of altered cortex in areas 17 and 18, neurons had receptive fields of normal locations and sizes. Thus, in the explored region of cortex, rows of recording sites extending mediolaterally from area 17 to area 18 produced rows of receptive fields systematically displaced from the last, forming a progression within the contralateral lower visual quadrant toward the zero vertical meridian as the border of areas 17 and 18 was reached, and back again for sites in area 18. Within the zone of altered cortex, neurons were activated by visual stimuli and had receptive fields of normal sizes. However, the receptive fields of these neurons were displaced from the region of the retinal lesion to adjacent parts of the retina (Fig. 1). Thus, for mediolateral rows of recording sites into the region of deprived cortex, receptive fields progressed from locations just temporal to the scotoma or "blind spot" produced by the lesion to the margin of the scotoma. Then, the progression of receptive fields ceased as the deprived cortex was reached. Receptive fields remained on the temporal side of the scotoma for several successive recording sites over 2 mm of cortex. Next, receptive fields jumped to the opposite side of the scotoma and remained stationary for several recording sites; they then resumed their normal progression for recording sites outside the deprived zone. In addition, some recording sites (Fig. 1, sites d/e in row 4) had two receptive fields, one on each side of the scotoma. The responsiveness of neurons with new receptive fields was not notably abnormal (*9*). Both area 17 and area 18 were altered in this way, and comparable results were obtained in four cats with retinal lesions of 5° to 10°.

An example of how progressions of receptive fields for rows of recording sites differed in normal and reorganized cortex is shown in Fig. 2. In normal cortex, receptive field centers shift systematically as recording sites progress across the retinotopic representation in area 17. In contrast, receptive fields for recording sites over a considerable tangential distance in cortex can have nearly the same receptive field center in reorganized cortex.

In two other cats, larger retinal lesions of 10° to 15° in diameter produced a larger zone of deprived cortex. In these cases, neurons near the margin of the deprived zone of cortex had displaced receptive fields, but neurons in a 2- to 3-mm-wide center of the deprived visual zone of cortex were unresponsive to visual stimuli. Thus, large zones of deprived cortex may not completely reorganize.

The present results (Fig. 1) indicate that portions of retinotopic cortical maps as large as 4 to 8 mm and encompassing 5° or more of the visual field can reorganize such that neurons within this cortex acquire receptive fields in new locations. Reorganization over such distances could result from changes in

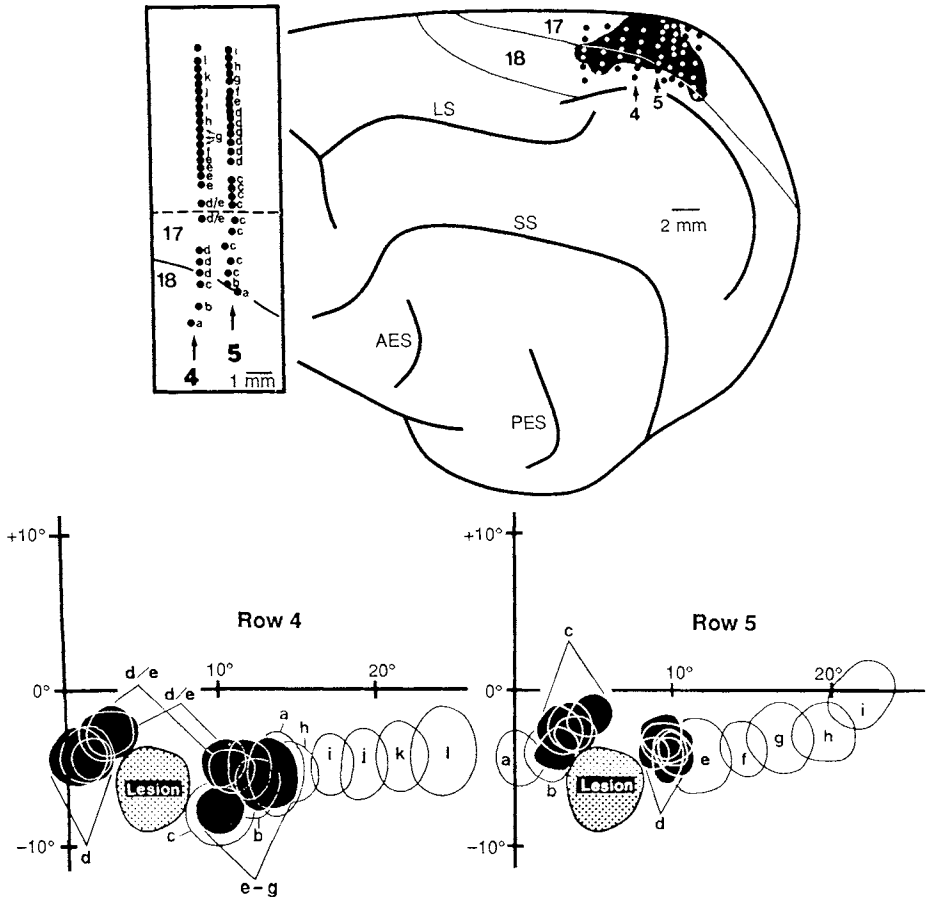

Fig. 1. Evidence for cortical reorganization from one case. Partial results are shown from a total of 121 recording sites, of which 55 produced abnormally located receptive fields and were judged to be within altered cortex. Shown are normal (outlined) and displaced (black) receptive fields for neurons at recording sites in areas 17 and 18 in a cat with a lesion of the retina of the right eye and enucleation of the left eye. Receptive fields were hand-plotted with projected, moving bars of light on a tangent screen or hemisphere (7). Some of the electrode penetrations producing mediolateral rows of recording sites are indicated by dots on a dorsolateral view of the brain on the upper right. The black region approximates the extent of the cortex where neurons had abnormally located receptive fields. Recording sites obtained from electrode penetrations of rows 4 and 5, including successive recording sites in penetrations extending down the medial wall of the cerebral hemisphere in area 17, are lettered in the box, a to l and a to i, respectively. The solid line in the box marks the estimated border of areas 17 and 18, and the dashed line marks the dorsal edge of the medial wall. The receptive fields for the lettered recording sites for each row are indicated in the contralateral hemifield depicted below. The zero vertical and zero horizontal meridians are marked in degrees of visual angle, and the projection of the retinal lesion (scotoma) is shown. Abbreviations: AES, anterior ectosylvian sulcus; LS, lateral sulcus; PES, posterior ectosylvian sulcus; and SS, suprasylvian sulcus. The normal organizations of areas 17 and 18 in cats are given in (*1*).

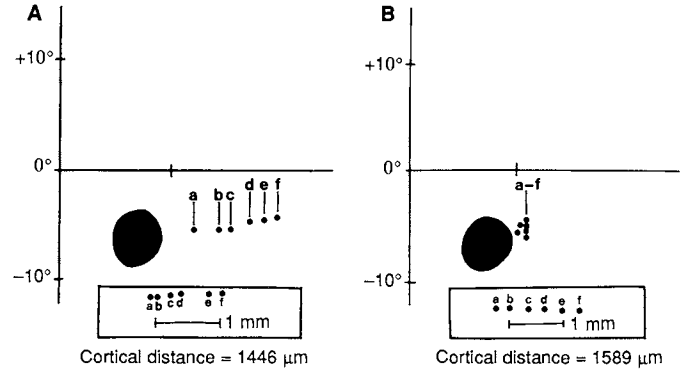

Fig. 2. Receptive field centers for recording sites in normal (**A**) and reorganized (**B**) parts of area 17. (A) Receptive field centers (a to f) systematically progress toward peripheral vision for a row of recording sites (a to f, box) moving away from the border of areas 17 and 18 in a part of area 17 that had normal retinotopic organization. (B) A similar row of recording sites in the part of area 17 that was deprived of normal activation by the retinal lesion produced an accumulation of receptive fields with nearly identical centers next to the blind area produced by the retinal lesion. In (A) and (B) horizontal and vertical meridians through the center of gaze are marked in degrees of visual angle in the visual hemifield contralateral to recording sites. Recording sites progress away from the border of areas 17 and 18 in area 17 (they are reversed from actual order in the left cerebral hemisphere for ease of matching the progressions of receptive fields and recording sites). The projection of the retinal lesion into the visual hemifield is in black.

the effectiveness of synapses within the arbors of thalamocortical axons of previously existing inputs (*10*). Comparable results have been obtained by Heinen and Skavenski (*11*) from part of area 17 of one monkey. Cortex with neurons initially unresponsive to visual stimuli after bilateral lesions of the fovea later contained neurons responsive to visual stimuli. Results from visual cortex are similar to those obtained from somatosensory cortex of monkeys; removing the inputs from part of the hand produces a zone of altered cortex where neurons achieve new receptive fields of normal sizes in other parts of the hand (*4, 5*). Furthermore, removing inputs from more than half of the hand produces a larger zone of deprived cortex where complete reactivation does not occur (*12*).

These results are important for at least two reasons. First, in certain ocular diseases in humans, lesions are commonly found in the retinas of both eyes, and retinotopic reorganization of visual cortex could result when lesions in the two eyes correspond to the same locations in visual space (*13*). Second, the present results, together with those from the somatosensory system, imply that basic neuronal properties such as receptive field location are maintained in a dynamic state in sensory-perceptual systems of adult mammals. Such adult plasticity may be important, not only in recoveries from brain damage and adjustments to other impairments, but also in our abilities to maintain, alter, and improve sensorimotor and perceptual skills.

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6. A single photocoagulation lesion was made with an Argon blue-green laser (Argon Medical, Athens, TX) (spot size, 500 μm; intensity, 2.5 W; duration, 5 s or longer) in the superior and nasal retina of one eye in cats anesthetized intramuscularly with ketamine hydrochloride (20 mg/kg) and xylazine (4 mg/kg). Within a few days, the contralateral eye was enucleated under Nembutal anesthesia (35 mg/kg, intraperitoneally) by standard procedures and under aseptic conditions. The animals were treated with antibiotics and maintained for 2 to 6 months before recordings were made.
7. Although cats have ocular dominance columns and some neurons in layer IV respond exclusively to one or the other eye, most neurons can be activated by either eye [for example, D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **160**, 106 (1962); *J. Neurophysiol.* **28**, 229 (1965)].
8. Recordings were largely from neuron clusters 800 to 1200 μm from the surface in the hemisphere contralateral to the lesioned eye. Penetrations were typically placed 200 to 300 μm apart in mediolateral rows about 1 mm apart. Recording sites in penetrations along layers in cortex of the medial wall were typically 100 μm apart. Recording methods were standard and have been described in detail elsewhere [J. H. Kaas and R. W. Guillery, *Brain Res.* **59**, 61 (1973); Y. M. Chino, M. S. Shansky, W. L. Jankowski, F. A. Banser, *J. Neurophysiol.* **50**, 265 (1983); Y. M. Chino, W. H. Ridder, E. P. Czora, *Exp. Brain Res.* 72, 264 (1988)]. Briefly, in one series of experiments, four cats were anesthetized with an initial dose of urethane (100 mg per 100 g of body weight, intraperitoneally), and the eye was mechanically stabilized. In a second series, two cats were initially immobilized with ketamine hydrochloride (20 mg/kg) and anesthetized with Fluothane and a mixture of 70% nitrous oxide and 30% oxygen. During the experiment, Fluothane was replaced by the intravenous infusion of Surital. These cats were paralyzed with an intravenous mixture of gallamine triethiodide (5 mg/kg per hour), *d*-tubocurarine (0.5 mg/kg per hour), atropine, and saline and were artificially respired. Both procedures produced similar results. The expired CO_2, blood pressure, electrocardiogram, and electroencephalogram were continuously monitored. Cycloplegia was maintained with 10% Neo-Synephrine and atropine sulfate, and the corneas were protected with gas-permeable contact lenses of appropriate curvature. The optic disc and the area centralis were projected onto a translucent plastic hemisphere or tangent screen. Much of the visual cortex of the dorsal surface of the brain was exposed, and the brain was protected in a chamber filled with silicone fluid. The exposed area was photographed with a scale to later record mapping sites and the sequence of mapping during the experiment. The surface pattern of blood vessels was used as a reference for establishing the position of each penetration. Recordings were made with low-impedance tungsten microelectrodes from clusters of neurons, and projected bars of light served as stimuli. Successive recording depths along penetrations down the medial wall were measured from the surface and from small electrolytic marker lesions placed along penetrations.
9. The response characteristics of recorded neurons were not quantitatively determined, but responses to moving bars of light appeared to be similar for neurons in and outside of the deprived zone of cortex.
10. Terminal arbors of thalamocortical axons in areas 17 and 18 of cats range from 1 to 3.5 mm in tangential width of distributions [A. L. Humphrey, M. Sur, D. J. Uhlrich, S. M. Sherman, *J. Comp. Neurol.* **233**, 159 (1985); *ibid.*, p. 190. Tangential axon collaterals of cortical neurons [C. D. Gilbert and T. N. Wiesel, *Nature* **280**, 120 (1979)] could also play a role.
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13. For example, patients who develop bilateral macular degeneration typically experience a permanent central scotoma of varied sizes. These patients use an eccentric retinal locus outside the scotoma for fixation, suggesting that such retinal areas act like a newly developed fovea for resolving spatial details [G. K. von Noorden and G. Mackensen, *Am. J. Ophthalmol.* **53**, 642 (1962); G. T. Timberlake *et al.*, *Invest. Ophthalmol. Visual Sci.* **27**, 1137 (1986); G. T. Timberlake, E. Peli, E. A. Essock, R. A. Augline, *ibid.* **28**, 1268 (1987)].

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