experiment. Her response was equivocal because the experiment was interrupted and also because she had a history of rapid cycles.

Conclusions drawn from responses of a small number of patients to a phase-shift experiment cannot be generalized. Nevertheless, our results support the hypothesis that disturbances in a central circadian pacemaker are involved in the pathophysiology of some types of depression and raise the possibility of new nonpharmacological treatment of the illness.

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16. The device is completely self-contained and records in solid-state memory the percentage of time during 15-minute sampling intervals during which patients' movement exceed a threshold. Periodically, a computer was used to retrieve, compile, analyze, and plot the data [T. R. Colburn, B. M. Smith, J. J. Guarini, N. N. Simmons, *International ISA Biomedical Sciences Instrumentation Symposium Publ. BM 76322* (1976), p. 117; *14, 17*].
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22. Since patients sometimes spontaneously switch out of the depressive phase of their illness, it is possible that the depressive remissions that occurred after experimental phase shifts were coincidental. Detailed clinical records demonstrated that the patient tended to remain indefinitely depressed when not treated with medications. Four previous untreated depressive episodes all exceeded 70 days and ended only when antidepressant medications were prescribed.
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25. We thank T. Colburn and B. Smith for developing, producing, and maintaining the activity monitoring devices used in this study, and W. Vaughn for computer programs used to process and display the activity data. A.W.-J. is a visiting Fellow of the Swiss Foundation for Biomedical Research.

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Functional Organization of Lateral Geniculate Cells Following Removal of Visual Cortex in the Newborn Kitten

Abstract. *When the visual cortex of a newborn kitten is removed, most neurons in the dorsal lateral geniculate nucleus degenerate, but a small population of large cells is spared. Electrophysiological recording revealed that detailed visual topography in the nucleus is abnormal and that single cells have unusually large receptive fields. These results suggest that optic axons deprived of their normal synaptic targets rearrange their connections to converge on local surviving neurons.*

The visual cortex of the cat receives a direct input from the dorsal lateral geniculate nucleus (LGN) of the thalamus. If areas 17, 18, and 19 of the visual cortex are removed in the adult cat, neurons in the LGN that relay information from the retina to the cortex undergo retrograde degeneration (*1*). By contrast, if a similar lesion is made in the newborn kitten, some of the neurons in the LGN survive the operation and do not degenerate (*2, 3*). Figure 1A shows a frontal section through the LGN of an adult cat in which most of areas 17, 18, and 19 of the visual cortex had been removed at birth. Although almost all of the cells in the nucleus have degenerated, large surviving neurons can be seen. These spared cells (Fig. 1B) are scattered throughout the LGN and are especially prominent ventrally in the vicinity of the C layers (*4*).

Since large surviving LGN neurons are rarely seen after damage to areas 17, 18, and 19 in the adult, we wondered if their presence in the cat operated on as an infant might represent an example of neuronal plasticity in which both structure and function are spared. We there-

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fore made large unilateral lesions of the visual cortex in five kittens on the day of birth (*5*). The animals were raised to adulthood under normal laboratory conditions and then prepared for extracellular recording of single LGN neurons according to conventional procedures (*6*).

Control recordings were made from the intact LGN of each brain, and we sampled a total of 30 single cells from the degenerated LGN ipsilateral to the early cortical lesion. All units included in this sample displayed action potentials typical of cell bodies (*7*), and histological reconstruction of the brains confirmed that each cell ipsilateral to the early lesion had been recorded during an electrode penetration through a degenerated section of the LGN (*8*). Given that most of the neurons in the degenerated LGN were severely shrunken with diameters less than 5 μm, it is reasonable to assume that most of our recordings were made from the large surviving cells, which average 30 μm in diameter. We used a small projector to map the receptive field of each cell with flashing or moving spots, slits, and annuli of various sizes. Stimulus intensity was fixed at approximately 1.0 log unit above a background illumination of 0.5 cd/m^2.

In the LGN of the normal adult cat, most cells are driven monocularly and have concentric center-surround receptive fields (*9*). The diameters of the centers of the receptive fields vary with eccentricity in the visual field. They are smallest, 0.25° to 1.0°, for cells that represent central vision and about double that for cells with receptive fields in the visual field periphery (*10*). Aside from a small nasotemporal overlap of approximately 2°, which results from a bilateral projection of the retina along the vertical meridian, neurons in the LGN map the contralateral visual field in a precise retinotopic fashion (*11*).

Two LGN cells ipsilateral to the early visual cortex lesion were not responsive to stimulation, but the rest were driven monocularly (17 by the contralateral eye, 11 by the ipsilateral eye), and most had a center-surround receptive field organization resembling that of normal control neurons. We encountered on- and off-center cells about equally; of 21 neurons tested, 18 had antagonistic surrounds. In about half of these cells, responses could be elicited when large spots or annuli were presented to the surround region alone; the remainder had silent surrounds that suppressed responses to center stimulation.

Despite the basic integrity of receptive field organization, cells in the degenerated LGN were markedly abnormal with regard to receptive field size and topography. Figure 2A shows the sizes of receptive field centers and locations in the visual field of ten LGN cells recorded from one cat. As in the normal cat, the smallest receptive field centers tended to lie centrally in the visual field and the largest peripherally, but the relation of the size of the receptive field center to eccentricity was not precise, in that some cells with receptive fields located centrally (for example, unit 13) had larger field centers than those at more peripheral positions. Regardless of location, however, the centers of receptive fields of cells in the degenerated LGN were dramatically larger than those in normal animals. The smallest receptive field center that we mapped was 3° in diameter, which is about the same size as the largest receptive field centers generally observed in the normal LGN (*10*). As a group, receptive field centers of LGN cells in cats operated on as infants had a mean diameter of 7.2° ± 0.7° (range 3° to 16°). In the normal cat, the mean diameter of receptive field centers is less than 2° (*10*).

These large field sizes suggest that single LGN cells receive converging input from widespread areas of the retina. In five neurons, an apparent convergence of even greater magnitude could be demonstrated outside the receptive field center. One of these cells, an on-center unit with low spontaneous activity (Fig. 2B), responded optimally to a 15° flashed spot (trace ii); it displayed only weak inhibition when the spot size was increased to 40°, even though a reliable off discharge was evoked from the receptive field surround (trace iii). Although this cell did not respond to flashed spots outside of its center-surround region, it produced vigorous time-locked discharges to a 10° moving spot anywhere in the contralateral hemifield (trace iv). In fact, the cell showed the same phasic discharges to a moving spot in the ipsilateral hemifield at locations as far as 20° from the zero vertical meridian.

Of the four remaining cells, one was an off-center unit organized similarly to that just described, except that it was not sensitive to movement in the ipsilateral hemifield. The other three cells were not excited by wide-field stimulus movement, but were clearly abnormal because they responded to flashed spots over much of the visual field. Two of these units had concentric center-surround receptive fields, one showing strong inhibition from a silent surround, the other

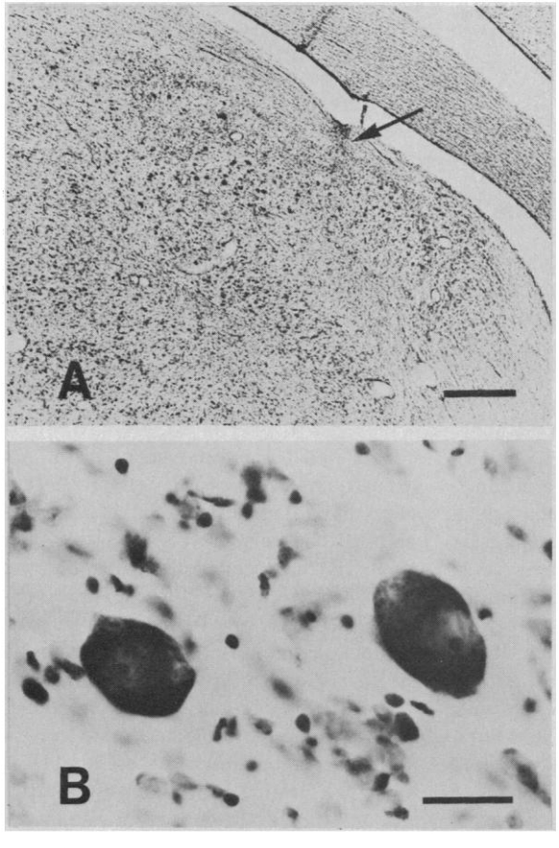

Fig. 1. (A) A frontal section through the middle third of the lateral geniculate nucleus in an adult cat (KVC-16) from which the visual cortex had been removed at birth. The LGN is severely degenerated, but large surviving cells are present throughout the nucleus. Arrow, area of gliosis marking the location of one electrode track. Scale, 0.5 mm. (B) Large surviving cells in laminae A and A1 surrounded by small shrunken neurons and glial cells. Scale, 25 μm.

weak inhibition from a surround with a clear off response when stimulated with an annulus. Outside of their immediate surround regions both cells responded to flashed spots throughout the contralateral hemifield and beyond 20° into the ipsilateral hemifield. The third cell (on-center) did not have a concentric surround but was flanked on one side by a region that inhibited response to center stimulation and produced an off response when stimulated separately. Throughout most of the contralateral hemifield and as far as 30° ipsilaterally, flashed spots elicited mixed on-off responses from this cell (*12, 13*).

Grossly, visual topography in the degenerated LGN appeared normal. When the microelectrode was moved from medial to lateral in the nucleus, receptive fields shifted from central to peripheral in the visual field. Similarly, a change from rostral to caudal in the position of the electrode was accompanied by movement of receptive fields from the inferior to the superior visual field. In contrast to the normal cat, however, small changes in microelectrode position frequently resulted in large and sometimes erratic shifts in receptive field location (penetrations III and IV in Fig. 2A). In penetration IV, the first cell encountered, unit 11, was driven by the contralateral eye, and its receptive field was located in the superior ipsilateral hemifield. After advancing the microelectrode only 5 μm, we recorded from unit 12, also driven by the contralateral eye, with a receptive field at the same eccentricity as unit 11, but 40° lower in the visual field. The last cell in the penetration, unit 13, was 250 μm from unit 12 and responded to the ipsilateral eye. Its receptive field was in the normal contralateral hemifield 30° from unit 12. Thus, in a short electrode penetration of 300 μm, we found nearby cells with receptive fields that were not only spatially distant from each other, but also included locations in both hemifields. In the normal LGN, receptive fields of adjacent cells tended to be superimposed and to remain in register when laminar borders were crossed (*11*).

Our results demonstrate that many LGN neurons that survive neonatal ablation of the visual cortex maintain functional synaptic connections with the retina. Basic receptive field organization and gross visual topography are preserved, but receptive field sizes are unusually large, and fine-grain topography is frequently abnormal. During the first postnatal month, immature LGN cells have large receptive field centers and weak surrounds (*14*). These response properties resemble those we have observed and suggest that early damage to the visual cortex may upset the normal functional development of LGN cells, leaving those which survive in a permanent state of immaturity. This can be only a partial explanation of our results, however, since visual topography in the infant LGN is completely normal, and individual cells are not sensitive to wide-field stimulation (*14*).

In view of the massive retrograde degeneration of LGN cells following neonatal removal of visual cortex, it is reasonable to assume that most postsynaptic sites in the LGN normally occupied by optic axons are effectively removed. As a result, retinal axons deprived of synaptic sites may seek new target cells and converge on surviving LGN neurons, providing inputs to them that originate from a much wider area of the retina than is customary (*15*). In establishing new contacts, afferents from the retina appear to make certain mistakes and avoid others. Thus, at the level of the single cell, visual topography is disturbed because adjacent cells sometimes receive input from disparate parts of the retina. By contrast, we never recorded from a binocularly driven LGN cell, which indicates that convergence of contralateral and ipsilateral afferents is avoided.

A futher consideration is that, after an early lesion is made in the visual cortex, medium-sized retinal ganglion cells that project to the degenerated LGN undergo severe retrograde transneuronal degeneration (*3*). Some geniculate cell abnormalities may thus be due to a reorganization of input from the retina arising from the convergence of bipolar and amacrine neurons on surviving retinal ganglion cells. This reorganization might explain the unusual sensitivity of several LGN cells to stimulation in the ipsilateral hemifield, since a weak influence, presumably the result of retinal mechanisms, has been reported in the normal cat (*13*).

Previous demonstrations of plasticity in the mammalian brain have shown that axons may sprout new terminals to invade deafferented sites or redirect their projection to new territories when appropriate target tissues are removed (*16*).

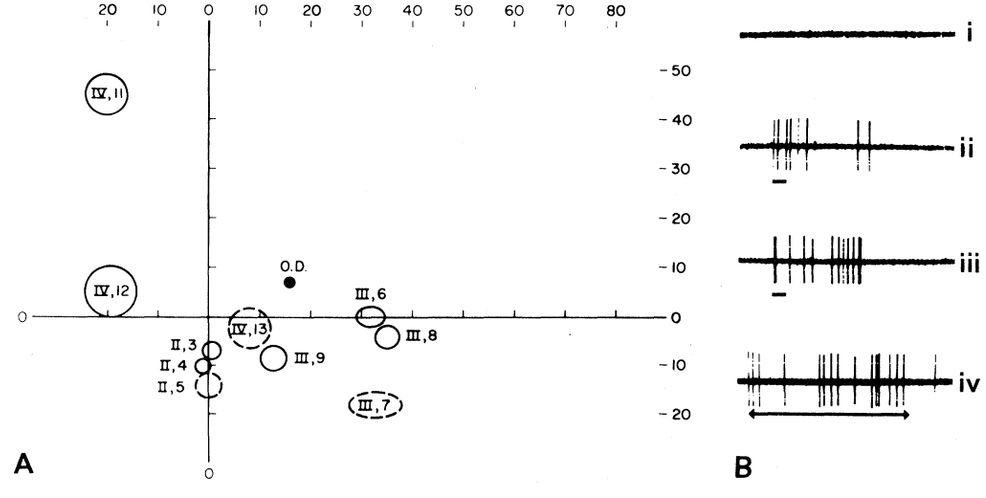

Fig. 2. (A) Map of receptive field center sizes and locations of ten cells recorded from the degenerated LGN of cat KVC-16. The solid lines indicate the 0° horizontal and vertical meridians. The ipsilateral hemifield is to the left of the vertical line, the contralateral field to the right. Penetration and unit numbers are indicated by Roman and Arabic numerals, respectively. Dashed lines show cells driven by the ipsilateral eye; solid lines, cells driven by the contralateral eye. Receptive field locations of cells driven by the ipsilateral eye have been transposed to make a single position of the optic disk (*O.D.*) appropriate for both eyes. All center diameters are abnormally large, and cells recorded in sequence in a given penetration often show widely scattered receptive field locations. (B) Activity of a neuron in the degenerated LGN responsive to wide-field stimulus movement. Receptive field center diameter is 15°. Each trace is approximately 4 seconds. Trace i, spontaneous activity. Trace ii, on response to a 15° spot flashed for 300 msec in the center of the receptive field. Trace iii, weak inhibition of the on-center discharge by a 40° flashed spot covering the receptive field center and surround. Trace iv, discharge coupled to the local back-and-forth movement (double-headed arrow) of a 10° spot in the periphery of the contralateral hemifield.

Our results suggest a new form of plasticity in that axons deprived of normal terminal sites, by the subtotal degeneration of cells in a target nucleus, shift their connections to local surviving neurons. Indeed, the hyperinnervation of selected neurons may itself play a role in determining which cells survive and which die.

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5. Since gyral patterns in the newborn kitten are poorly developed, we made large lesions to remove most of the cortex of the presumptive lateral, postlateral, and splenial gyri, but spared that of the suprasylvian gyrus. It is difficult to reconstruct precisely the extent of such large lesions made in neonatal brains because, during development, remaining adjacent cortical tissue is always disrupted and often assumes a bizarre configuration. We therefore estimated the size of each lesion on the basis of the severity and extent of retrograde degeneration in the LGN. In three of the five cats, the intended lesion was incomplete. One animal showed some surviving cells of all sizes throughout the LGN, and in two cats the rostral pole of the LGN was spared, although the rest of the nucleus was severely degenerated. The lateral geniculates in the two remaining cats were, with the exception of large surviving cells, completely degenerated, which indicates that the lesion in each case probably removed all of areas 17, 18, and 19. Cells recorded from these two cats represented about 65 percent of our sample and displayed the most striking abnormalities.
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8. At the end of each experiment, the animal was perfused through the heart with 10 percent Formol-saline. The brain was blocked in the frontal plane and 40-μm frozen sections through the LGN and visual cortex were collected serially and stained with cresyl violet for cell bodies. Care was taken to locate each electrode track to ensure that all cells in our sample had been recorded from degenerated regions of the laminated part of the LGN and not from the medial interlaminar nucleus or the ventral lateral geniculate. Recording sites were identified by the location of small marking lesions that had been made with the microelectrode or by comparing the micrometer reading of each unit's depth below the cortical surface (as noted during the experiment) with measured distance along the reconstructed electrode track.
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12. Receptive fields of the five cells with wide-field sensitivity were mapped with a low-intensity stimulus to avoid an artifact resulting from stray light. Although it is not possible to exclude a relation between the wide-field responses we have observed and McIlwain's (*13*) periphery effect in normal LGN cells, our findings are clearly different. When contrast outside of the receptive field is varied by local stimulus movement, cells showing the periphery effect display a lowered threshold to center stimulation or a gradual increase in maintained discharge, but, in contrast to our results, they do not give direct, sharply timed responses to the peripheral stimulus [B. G. Cleland, M. W. Dubin, W. R. Levick, *J. Physiol. (London)* **217**, 473 (1971); B. G. Cleland *et al.*, in (*9*)].
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15. This view is strengthened by anatomical studies of the retinogeniculate pathway in cats operated on as infants (*3*), which show that axons from the retina often run orthogonal to the lines of projection in the LGN and form exceptionally dense terminal fields in the immediate vicinity of large surviving neurons.
16. For review, see R. D. Lund, *Development and Plasticity of the Brain* (Oxford Univ. Press, New York, 1978).
17. Supported by NIH grants EY01331 (R.K.) and EY01122 and EY02488 (E.H.M.). We thank R. W. Guillery and P. D. Spear for helpful comments.
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Molecular Microanalysis of Pathological Specimens in situ with a Laser-Raman Microprobe

Abstract. *A laser-Raman microprobe has been used to identify microscopic inclusions of silicone polymer in standard paraffin sections of lymph node. This example of organic chemical microanalysis in situ in pathological tissue represents an extension of microanalytical capabilities from elemental analysis, performed with electron and ion microprobes, to compound-specific molecular microanalysis.*

We report here the successful application of micro-Raman spectroscopy to the detection and identification of complex silicone polymer fragments in standard tissue sections. This technique, developed recently in two laboratories (*1*, *2*), offers exciting new prospects for biological studies by providing nondestructive compound-specific molecular microanalysis with good spatial resolution and high sensitivity to principal molecular components. A major weakness of current techniques [employing electron (*3*), proton (*4*), and ion (*5*) beam instruments with x-ray or secondary ion analysis] has been their general limitation to inorganic and elemental rather than organic and compound identification.

The instrument we used, which was developed at the National Bureau of

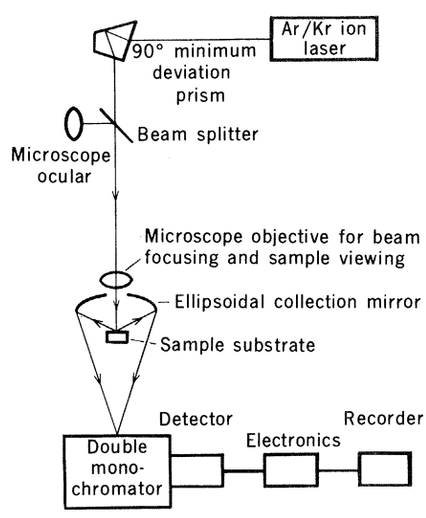

Fig. 1. Schematic diagram of the laser-Raman microprobe developed at the National Bureau of Standards. Any one of several laser wavelengths in the visible region of the spectrum is used to excite the micro-Raman spectrum. Nonlasing plasma lines are removed by use of a predispersing prism. The radiation scattered by the sample is collected over a large solid angle in 180° backscattering geometry. Lateral spatial resolution of the probe measurement is determined by the spot size of the laser on the sample and a spatial filter (exit pinhole, not shown) placed in the path of the collected scattered light. Depth resolution is several micrometers (but less than ~ 12 μm), depending on the optical transparency and surface topography of the sample. Typical measurement parameters employed in the microanalysis of thin sections of biological soft tissue are: laser wavelength, 514.5 nm (green) and 647.1 nm (red); laser power, 5 to 60 mW (at sample); laser spot diameter, 6 to 20 μm; time constant, 1 to 5 seconds; scan rate, 50 to 10 cm^{-1} per minute; and spectral slit width, 3 cm^{-1}.

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