3. J. Glowinski and J. Axelrod, *Pharmacol. Rev.* **18**, 775 (1966).
4. S. M. Schanberg, J. J. Schildkraut, I. J. Kopin, *Biochem. Pharmacol.* **16**, 393 (1967); J. J. Schildkraut, S. M. Schanberg, G. R. Breese, I. J. Kopin, *Amer. J. Psychiat.* **124**, 600 (1967).
5. J. J. Schildkraut, G. A. Dodge, M. A. Logue, *J. Psychiat. Res.* **7**, 29 (1969).
6. J. J. Schildkraut, *Fed. Proc.* **28**, 795 (1969).
7. S. M. Schanberg, J. J. Schildkraut, I. J. Kopin, *J. Pharmacol. Exp. Ther.* **157**, 311 (1967). The amount of [^{3}H]norepinephrine injected intracisternally was constant in any given experiment but varied between experiments.
8. A. H. Anton and D. F. Sayre, *J. Pharmacol. Exp. Ther.* **138**, 360 (1962); L. G. Whitby, J. Axelrod, H. Weil-Malherbe, *ibid.* **132**, 193 (1961); I. J. Kopin, J. Axelrod, E. Gordon, *J. Biol. Chem.* **236**, 2109 (1961); S. M. Schanberg, J. J. Schildkraut, G. R. Breese, I. J. Kopin, *Biochem. Pharmacol.* **17**, 247 (1968); J. J. Schildkraut, *Amer. J. Psychiat.* **126**, 925 (1970).
9. J. J. Schildkraut, P. R. Draskoczy, A. Winokur, in preparation.
10. F. Javoy, A. M. Thierry, S. S. Kety, J. Glowinski, *Commun. Behav. Biol. Part A*, **1**, 43 (1968).
11. N. H. Neff and E. Costa, in *Antidepressant Drugs*, S. Garattini and M. N. G. Dukes, Eds. (Excerpta Medica, Amsterdam, 1967), p. 28.
12. J. J. Schildkraut, G. L. Klerman, R. Hammond, D. G. Friend, *J. Psychiat. Res.* **2**, 257 (1964).
13. J. J. Schildkraut, E. K. Gordon, J. Durell, *ibid.* **3**, 213 (1965).
14. A. Carlsson and M. Lindqvist, *Acta Pharmacol. Toxicol.* **20**, 140 (1963); N. E. Andén, B.-E. Roos, B. Werdinius, *Life Sci.* **3**, 149 (1964); R. Laverty and D. F. Sharman, *Brit. J. Pharmacol. Chemother.* **24**, 759 (1965); M. Da Prada and A. Pletscher, *Experientia* **22** 465 (1966); H. Corrodi, K. Fuxe, T. Hökfelt, *Life Sci.* **6**, 767 (1967); H. Nybäck, G. Sedvall, I. J. Kopin, *ibid.*, p. 2307; W. Dairman, R. Gordon, S. Spector, A. Sjoerdsma, S. Udenfriend, *Mol. Pharmacol.* **4**, 457 (1968).
15. Uptake into the presynaptic neuron is thought to be the major mechanism for terminating the physiological activity of extraneuronal norepinephrine. A fraction of norepinephrine present extraneuronally escapes reuptake, however, and is converted to normetanephrine. The concentration of normetanephrine may thus reflect the concentration of norepinephrine discharged extraneuronally onto receptors [J. Axelrod, *Pharmacol. Rev.* **18**, 95 (1966); I. J. Kopin, *ibid.*, p. 513].
16. G. C. Sedvall, V. K. Weise, I. J. Kopin, *J. Pharmacol. Exp. Ther.* **159**, 274 (1968).
17. A. J. Prange, Jr., I. C. Wilson, A. M. Rabon, M. A. Lipton, in *The Present Status of Psychotropic Drugs, Proceedings of the 6th International Congress of the CINP, Tarragona, Spain, April 1968*, A. Cerletti, Ed. (Excerpta Medica International Congress Series, No. 180, Amsterdam, 1969), p. 532; A. J. Prange, Jr., I. C. Wilson, A. M. Rabon, M. A. Lipton, *Amer. J. Psychiat.* **126**, 457 (1969).
18. A. Winokur, A. M. Soto, P. R. Draskoczy, J. J. Schildkraut, in preparation.
19. J. J. Schildkraut, *Neuropsychopharmacology and the Affective Disorders* (Little, Brown, Boston, in press); ———, R. Green, E. K. Gordon, J. Durell, *Amer. J. Psychiat.* **123**, 690 (1966).
20. Supported in part by PHS grant MH 15,413 from the National Institute of Mental Health, by a grant from Merck Sharp & Dohme, and by the Supreme Council, 33° Scottish Rite, Northern Masonic Jurisdiction, U.S., fellowships to medical students A.W. and C.W.A. We thank Geigy Pharmaceuticals for the imipramine and Merck Sharp & Dohme for the protriptyline used in these studies.

22 December 1969; revised 24 February 1970 ■

Visual Experience Modifies Distribution of Horizontally and Vertically Oriented Receptive Fields in Cats

Abstract. *Cats were raised from birth with one eye viewing horizontal lines and one eye viewing vertical lines. Elongated receptive fields of cells in the visual cortex were horizontally or vertically oriented—no oblique fields were found. Units with horizontal fields were activated only by the eye exposed to horizontal lines; units with vertical fields only by the eye exposed to vertical lines.*

Many investigators have studied the response characteristics of single cells in the visual system in an effort to understand the neural mechanisms of perception (*1–4*). In the visual cortex of the cat and the monkey, there are units with elongated receptive fields which respond vigorously to elongated stimuli of the same orientation as the receptive field (*2–5*). It is frequently assumed that such units are important in the perception of form (*3, 6*), but no direct test of this hypothesis has been made (*7*). Ideally, one might remove all cortical units with receptive fields of a given orientation and observe the subject's visual capabilities. This would require ablation of cells on a physiological rather than an anatomical basis.

We have developed a technique for rearing kittens which results in all of the elongated receptive fields being oriented either vertically or horizontally, in contrast to the random arrangement present in normal cats (*3, 8*). Moreover, the units with horizontal fields respond only to stimulation of one eye, and the units with vertical fields respond only to stimulation of the other eye. Therefore, it should be possible to test the behavioral function of either class of cells by simply occluding one eye or the other.

We controlled the visual experience of kittens from birth until 10 to 12 weeks of age. Each animal's total visual experience consisted of viewing a white field containing three black vertical lines with one eye and, simultaneously viewing a field containing three horizontal lines with the other eye. The lines were 1 degree wide and their center points were 6 degrees apart. These conditions were used in order to produce discordant sensory input to the binocularly activated cortical cells.

The stimuli were mounted in a mask which provided a 50- to 60-degree field of view for each eye. Beginning at 3 weeks of age the animals wore these devices for approximately 8 hours a day. Masks were put on and removed inside a darkroom in which the animals were housed from birth whenever they were not wearing the masks. Each set of lines in the mask was positioned at the focal plane of a lens so that small changes in the position of the mask would not affect the sharpness of focus. The kittens soon became accustomed to the masks and were active and playful during the exposure periods. To insure that the animals could not pull or rub the masks off they wore a large neck ruff similar to that used by Hein and Held (*9*). The animals were checked repeatedly while they were wearing the masks. We estimate that slippage of the mask did not exceed 10 degrees and in most cases was less than 5 degrees; eye movements were not measured during exposure periods. It is clear from the positive results obtained that any rotations of the eyes or the mask did not interfere with the aim of the experiment.

Single unit recordings were made from the visual cortex of these animals between 10 and 12 weeks of age. We used the preparation, recording, and mapping technique developed by Spinelli (*10*). In brief, thiopental sodium was injected intravenously to obtain general anesthesia and a small opening was made in the skin, bone, and dura above the visual cortex in one hemisphere. Subsequently the animal was paralyzed with Flaxedil, artificially ventilated, and held in a stereotaxic instrument. All pressure points and incisions were infiltrated with a long-acting local anesthetic (Zyljectin). The cat was positioned at 57 cm from a white tangent screen; at this distance 1 cm on the screen is equal to 1 degree of arc at the eye. Contact lenses were used to correct for accommodation and to protect the cornea of the eye. The projection of the optic disk onto the screen was determined with a reversable ophthalmoscope, and the position of the area centralis was inferred (*11*). The estimated projections of the area centralis were centered at or near the top of the mapped region in four animals and about 5 degrees above in the remaining animal. The units were recorded from primary visual cortex between stereotaxic coordinates anterior-posterior −1.0 to +1.0 mm and medial-lateral 0.5 to 1.5 mm. In adult cats this corresponds

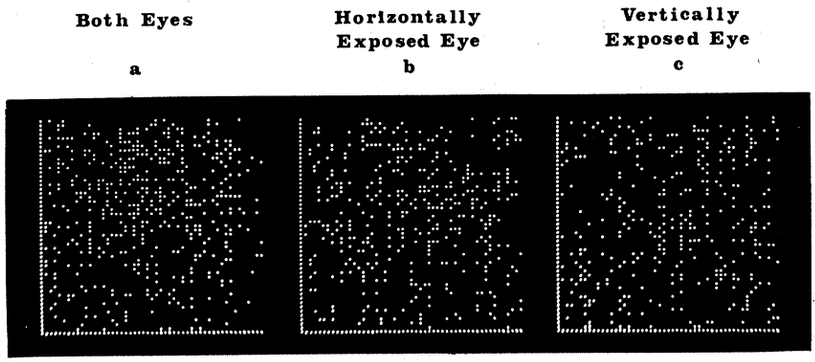

Fig. 1. Cortical unit with diffuse receptive field. Column a, Unit mapped with both eyes open; b, eye exposed to horizontal lines was left open; c, eye exposed to vertical lines was left open. The spot moved vertically during the mapping.

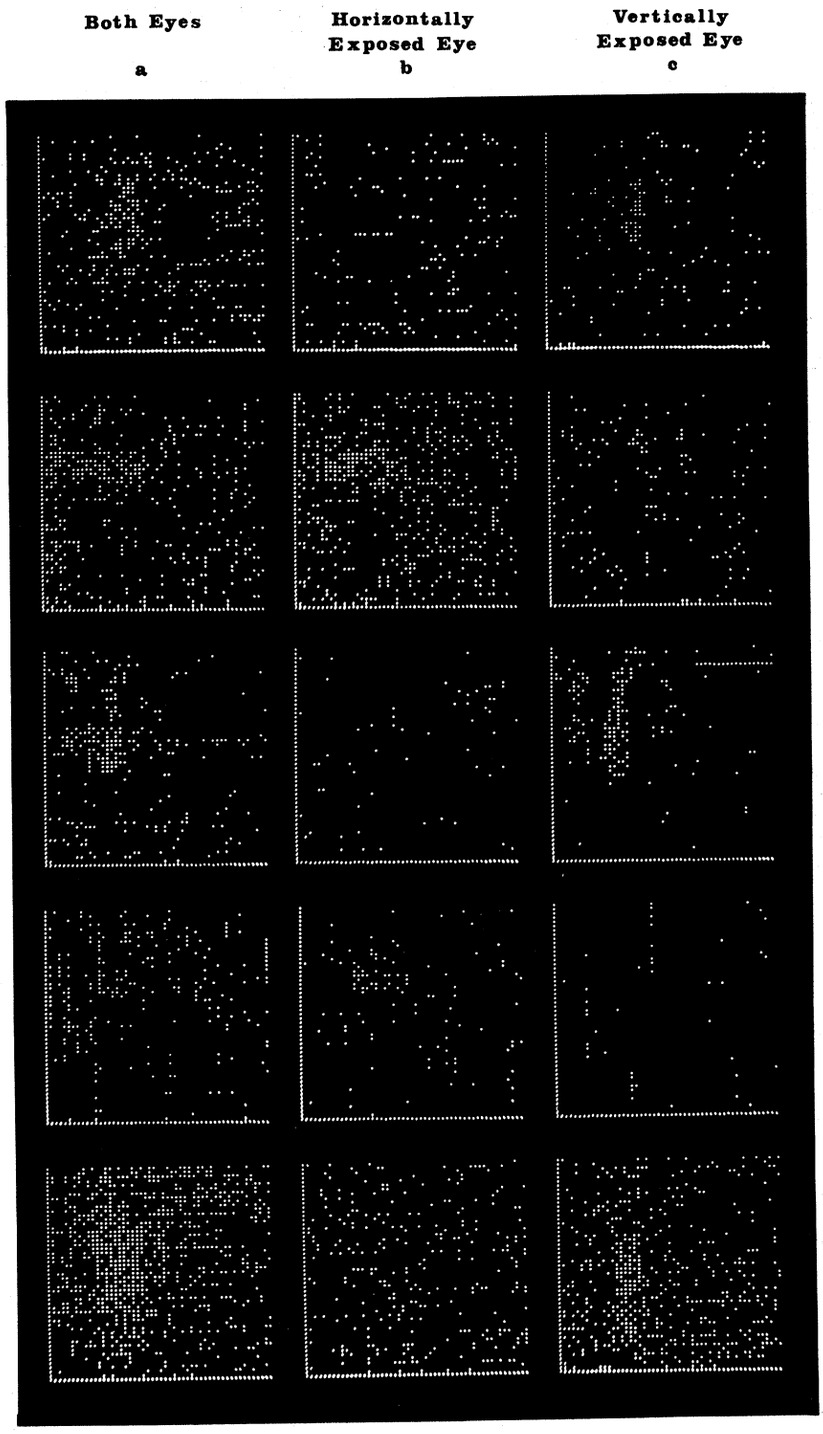

Fig. 2. Cortical units with elongated receptive fields. Rows 1 to 5 illustrate integral contour displays of receptive fields of five units. In column a, the units are mapped with both eyes open; b, units mapped with only the eye exposed to horizontal lines open; c, units mapped with only the eye exposed to vertical lines open. Rows 3 and 4 illustrate receptive fields from two units found in the same cat. Note that all receptive fields are elongated, that the units are activated by only one eye, and that the orientation of the receptive fields is identical to the orientation of the lines to which that eye was exposed during development. The unit illustrated in row 4 has one of the most poorly defined receptive fields found when mapped with both eyes open. It should, however, be noted that the receptive field is well defined when mapped with the horizontally exposed eye open (4b) whereas it is completely absent when mapped with the vertically exposed eye open (4c). During mapping the spot moved horizontally in rows 1, 3, and 5 and vertically in rows 2 and 4.

to the region that receives projections from the area centralis (*12*).

The response of single units to a black spot (1 to 4 degrees in diameter) moving across the white background was recorded with tungsten microelectrodes. We used spots rather than line stimuli in mapping because this method should reveal the shape of the receptive field with the least bias (*4*). Elongated receptive fields of single units in the visual cortex of the cat have been mapped with stationary (*3*) and moving (*4*) spots. The responsiveness to line stimuli can be predicted from maps made with spots, at least for units which have discrete excitatory and inhibitory regions within the receptive field [(*4*); simple cells (*3*)] and perhaps for other types of units [for example, complex cells, diffuse cells (*4*)].

The spot was moved by a computer (Digital Equipment Corp., PDP-8) across a 25- by 25-degree field. The unit's activity was recorded at each of 2500 points within this field and presented on an oscilloscope screen as an integral contour display. In this manner the shape of the receptive field could be visualized. All units encountered during the recording were analyzed and whenever possible each was mapped at least twelve times. The mapping was first done with both eyes open and

then for each eye separately. Two vertical and two horizontal maps were made for each of these conditions. During a vertical map, for example, the spot was moved with constant speed of 10 deg/sec from bottom to top and top to bottom; 50 such scans covered the field. Data were collected separately for upward and downward motion of the spot to provide the two vertical maps. Horizontal maps were also obtained in this fashion.

Currently, a total of 50 units from five animals have been mapped in detail. Receptive fields of all units were in the lower half of the visual field. All maps were examined, but categorization of the units was based largely on the receptive field map obtained with the spot moving in the direction which elicited the strongest response from the unit (*4*). Units encountered during the recording were classified as either diffuse or elongated. Diffuse receptive fields have no clearly defined boundaries, and the units responded to stimulation over a wide portion of the visual field. Twenty-seven units were of this type (Fig. 1).

Receptive fields from 23 units were categorized as elongated. Their shapes ranged from somewhat elliptic to clearly edge- or bar-shaped in correspondence with elongated receptive fields described by others. Whereas normal kittens have a full complement of receptive field orientations at birth (*13*) all of the elongated fields found in our animals were oriented either vertically or horizontally (Fig. 2). Since diagonally oriented receptive fields have been mapped in normal animals with our recording procedure [figure 7 in (*4*)], their absence here is not an artifact.

Three characteristics of these elongated receptive fields are striking when compared to elongated receptive fields found in normal cats. First, 21 of the 23 units with elongated receptive fields were predominantly or exclusively activated by only one eye, whereas normally only 10 to 20 percent of the units in the visual cortex of the cat respond to just one eye (*3*, *4*). The discordant stimulation of the two eyes might have produced this loss in binocularity (*14*). The remaining two units were lost before we could determine whether they were also monocular. Second, a particular eye could activate cortical units with receptive fields of only one orientation, either vertical or horizontal, although in the normal cat receptive fields of all orientations can be activated by both eyes. Furthermore, in 20 of these 21 monocular units, the receptive field orientation corresponded to the orientation of the lines to which the eye that activated the unit had been exposed during rearing. Figure 2, rows 3 and 4, for example, shows elongated receptive fields recorded from two units found in the same cat—one unit was activated only by the eye exposed to horizontal lines, and the other only by the eye exposed to vertical lines. Third, some of the elongated receptive fields were considerably larger than those present in normal cats (*3*, *4*).

The change in the distribution of orientations of cortical unit receptive fields that we found when kittens were raised with both eyes viewing different patterns demonstrates that functional neural connections can be selectively and predictably modified by environmental stimulation. Whether the discordant stimulation is a necessary condition is not known. A final aspect of our technique is that we succeeded in reviving our animals after the electrophysiological recording. Therefore, we can test the performance of these same cats in the discrimination of patterns and determine the behavioral effects of the physiological manipulation.

HELMUT V. B. HIRSCH*
Department of Psychology, Stanford University, Stanford, California 94305
D. N. SPINELLI
Department of Psychiatry, Stanford University

References and Notes

1. H. B. Barlow, R. M. Hill, W. R. Levick, *J. Physiol. London* **173**, 377 (1964); H. K. Hartline and F. Ratliff, *J. Gen. Physiol.* **41**, 1049 (1958).
2. G. Baumgartner, J. L. Brown, A. Schulz, *Neurophysiology* **28**, 1 (1965).
3. D. H. Hubel and T. N. Wiesel, *J. Physiol. London* **160**, 106 (1962).
4. D. N. Spinelli and T. W. Barrett, *Exp. Neurol.* **24**, 76 (1969).
5. D. H. Hubel and T. N. Wiesel, *J. Physiol. London* **195**, 215 (1968).
6. D. M. MacKay, in *Models for the Perception of Speech and Visual Form*, W. Walthen-Dunn, Ed. (MIT Press, Cambridge, 1967), pp. 25–43; W. R. A. Muntz, *ibid.*, pp. 126–136.
7. The following are examples of indirect tests of this hypothesis: L. Ganz and M. Fitch, *Exp. Neurol.* **22**, 638 (1968); R. W. Sekuler, E. L. Rubin, W. H. Cushman, *J. Opt. Soc. Amer.* **58**, 1146 (1968); T. N. Wiesel and D. H. Hubel, *J. Neurophysiol.* **26**, 1003 (1963); ———, *ibid.* **28**, 1029 (1965).
8. More recent data [J. D. Pettigrew, T. Nikara, P. O. Bishop, *Exp. Brain Res.* **6**, 373 (1968)] would suggest that near the visual axis vertically and horizontally oriented receptive fields may be more common than obliquely oriented receptive fields. Our observations on normal adult cats (D. N. Spinelli, unpublished data) would indicate that, whereas there is such a preference, its magnitude may be relatively small.
9. A. Hein and R. Held, *Science* **158**, 390 (1967).
10. D. N. Spinelli, *Exp. Neurol.* **19**, 291 (1967).
11. G. J. Vakkur, P. O. Bishop, W. Kozak, *Vision Res.* **3**, 289 (1963).
12. R. Otsuka and R. Hassler, *Arch. Psychiat. Nervenkrankh.* **203**, 212 (1962).
13. D. H. Hubel and T. N. Wiesel, *J. Neurophysiol.* **26**, 994 (1963).
14. ———, *ibid.* **28**, 1041 (1965).
15. We thank C. R. Hamilton for help and advice as the senior author's thesis adviser. Senior author supported by NIMH predoctoral fellowship 2-F1-MH-29-103. Support provided by PHS grants NB-06501 and MH-12970. B. Bridgman and R. Phelps assisted with the electrophysiological recording.
* Address after 15 June 1970: Department of Biophysics, Johns Hopkins University, Baltimore, Maryland.

29 December 1969; revised 27 February 1970

Physiological Responses of Infant Rats to Separation from Their Mothers

Abstract. *Decreases of 40 percent in cardiac and respiratory rates occur during the first 12 to 16 hours after 2-week-old rat pups are separated from their mothers. These rates decrease without significant alteration in activity level and despite maintenance of body temperature, of nutrition by intubation, of an intact litter, and of the home cage nest.*

There is increasing experimental evidence that immediate and prolonged behavioral responses occur in infant monkeys after interruption of the mother-infant relationship at certain early periods of development (*1*). Less obvious behavioral changes have been described after early separation in dogs and cats (*2*), but little attention has been paid to the possibility of separation responses occurring in mammals below this phylogenetic level. Few studies of early maternal deprivation have included physiological measurements; thus, the dimensions of the biological impact of such experiences are as yet unknown, although some interesting endocrine abnormalities have recently been reported in a clinical study of emotionally deprived human infants (*3*).

An earlier study from this laboratory on the development of cardiac rate regulation in rats prior to weaning (*4*) demonstrated a phase from day 7 to day 16 of postnatal life when resting heart rates in the home cage litter were maintained at relatively high levels compared with rates at 3 weeks of age or in adulthood. The present experi-