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"The Development of Maps and Stripes in the Brain"

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The Development of Maps and Stripes in the Brain

In the human brain nerve cells form maps of their relations with the external world, and the maps are divided into stripes. How the stripes form is explored by creating a frog with three eyes

by Martha Constantine-Paton and Margaret I. Law

The brain of a vertebrate animal is the most complex structure in any living organism. The versatility and analytical abilities of that structure are suggested under the microscope by the appearance of individual neurons, or nerve cells. Each such cell appears to be different from its neighbors in its elaborate form and its links with other neurons by means of synapses at the tips of its axon, or nerve fiber. There is nonetheless a remarkable consistency imposed on this diversity. As more is learned about the patterns of connectivity in various parts of the brain, principles of organization begin to emerge, raising the hope that the types of neuronal interactions underlying the apparent complexity will turn out to be manageably small in number.

One such principle of organization is mapping. The axons that project from neurons in one region of the brain to neurons in another region generally reproduce neighborhood relations. As a result if two neurons are neighbors in the first region, their synapses will form on the same cell or on neighboring cells in the second region: the target population. This regularity in axonal projections was initially detected in the 19th century. It has now been found in all the projections through which sensory signals reach the cerebral cortex, in the projections through which one area of the cerebral cortex is connected to another and in the projections through which the parts of the brain involved in the control of movement act on the muscles of the body.

A second principle of organization, much more recently recognized, is the partitioning of the regions of the brain that embody a map into periodic subdistricts. For example, work in the laboratory of Jon H. Kaas at Vanderbilt University has revealed a highly regular partitioning of the somatic sensory cortex: the part of the cerebral cortex that gets sensory data from muscles, joints and the skin. In the somatic sensory cortex the surface of the hand is represented by a map. Hence touching two points on the skin that are near each other elicits measurable electrical activity in groups of neurons that are neighbors in the cortex. In experiments with monkeys Kaas and his colleagues find that in the layer of the cortex where the entering axons make their synapses, designated Layer 4, the map is partitioned into bands. The bands separate sensory inputs from the hand according to the kinds of information the input carries. In some bands the neurons respond only to the onset of a touch; in the intervening bands the neurons have a more prolonged response. It is as if the map of the hand in the somatic sensory cortex of the monkey has been constructed by alternating stripes cut out of two distinct maps of the hand. One map (and one set of stripes) represents what are called rapidly adapting nerve endings in the skin; the other represents more slowly adapting nerve endings.

Edward G. Jones and his colleagues at the Washington University School of Medicine were among the first to demonstrate anatomically that such functional subdivisions arise because each subdivision receives particular axons. Jones and his colleagues employed a radiographic technique. They injected into the somatic sensory cortex on one side of the brain of a monkey a small quantity of amino acids labeled with tritium, the radioactive isotope of hydrogen. The amino acids were taken up by neurons in the cortex and transported down the axons projecting from some of those neurons to the somatic sensory cortex on the opposite side of the brain. There the labeled axons laid down a pattern of radioactivity that was detectable by coating slices of the tissue with a photographic emulsion sensitive to radioactivity.

The pattern of radioactivity in successive slices indicated that the axons terminate in a clearly delimited series of stripes. Thus inputs crossing from one side of the brain to the other as well as inputs carrying information from the skin terminate in stripes in the somatic sensory cortex. The partitioning of inputs to the somatic sensory cortex is not, however, the only example of striped patterns. There are many other examples. Stripes have been found in all sensory pathways, in many regions of the cerebral cortex and in regions of the brain as diverse as the superior colliculus, the cerebellum and the medulla oblongata.

Periodic synaptic zones that form functional stripes in a region of the brain that simultaneously embodies a map present a puzzle. Why are they there? Why should the brain establish an elaborate means of segregating various inputs when ultimately the inputs will converge to produce a unified representation? The two of us have done a series of experiments that suggests an answer to the question.

Our work focuses on the visual system, a set of projections that carry visual information from the retina to more central stations of the brain. These pathways have been studied intensively, and as a result more is known about the central nervous system's representation of the visual world than is known about the representation of any other sensory modality. Much of the work has been done, on the cat and the monkey, by David H. Hubel, Torsten N. Wiesel and their colleagues at the Harvard Medical School. Their results constitute a detailed analysis of the relation between topographic and functional organization. In the cat and the monkey the visual pathways convey information to the part of the cerebral cortex designated the visual cortex. The map there is binocular: it arises from axons delivering information from each of the animal's eyes. Hubel and Wiesel have found,

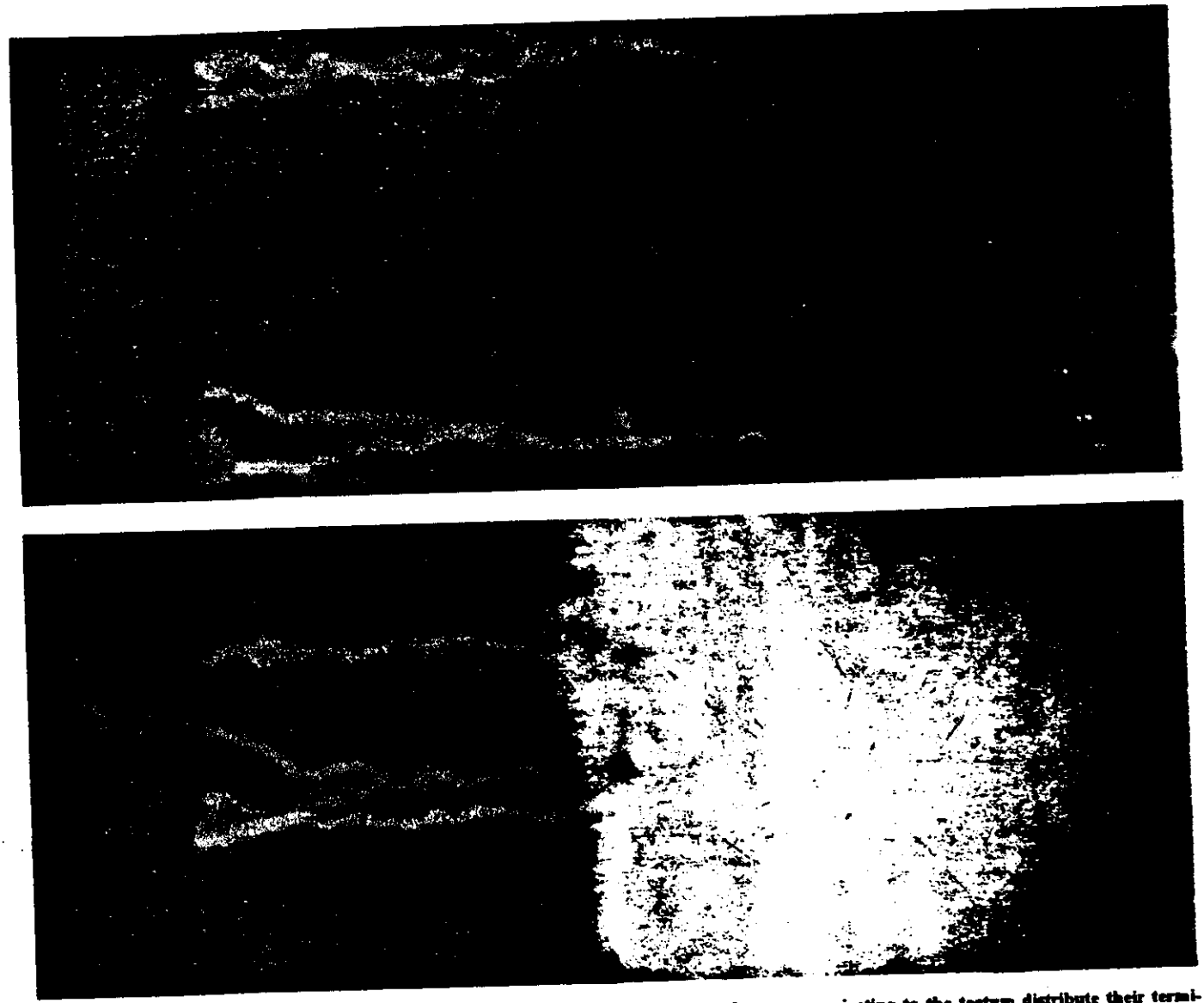
STRIPES IN A MAMMAL'S BRAIN are found in the visual cortex, the part of the cerebral cortex that gets data from the eyes. The tissue shown is about a fourth of the visual cortex on one side of the brain of a macaque monkey. One of the animal's eyes has been injected with a small quantity of an amino acid (proline) labeled with tritium, the radioactive isotope of hydrogen, and over a period of two weeks the radioactivity has been carried in axons, or nerve fibers, from the eye to the lateral geniculate nucleus of the brain and from there to the visual cortex. When slices of tissue from the visual cortex are coated with a photographic emulsion, the radioactivity exposes the emulsion in bright stripes. The stripes interdigitate with darker stripes representing the uninjected eye. Each stripe is about 350 micrometers wide. The image was provided by Simon LeVay of the Harvard Medical School; it is a montage produced from successive slices of tissue.

however, that when a microelectrode is passed through brain tissue in Layer 4 of the visual cortex, it records the electrical activity of neurons in a highly regular alternating sequence. An initial series of neurons might respond only to flashes of light in the animal's left eye. Then would come a series of cells responding only to the right eye, and then again a series of cells responding to the left.

Hubel, Wiesel and their colleagues have shown further that this functional alternation results from the segregation of the axons that carry information from each eye. The labeling of each eye's visual pathway with radioactive amino acids reveals stripes that run in a zebra-like pattern throughout Layer 4 of the visual cortex. Each stripe contains cells that respond exclusively to one eye, the left or the right. The cells in turn project their axons to binocular neurons in the cortical layers above and below them. In other words, every part of the visual world on which the cat or the monkey can train both of its eyes is represented twice in Layer 4: once at some point in a stripe of cells representing the left eye and again in a neighboring stripe representing the right eye.

Our own experiments at Princeton University capitalized on several properties of a considerably different visual pathway, that of the leopard frog (*Rana pipiens*). The experiments relied on a classical procedure of transplanting tissue in amphibian embryos. This transplantation, however, is combined with modern techniques of neuroanatomy and neurophysiology for examining the patterns of connections that neurons in the visual system make when they are placed in abnormal situations early in development. On occasion such analyses can reveal principles of growth and organization that are not obvious during normal development.

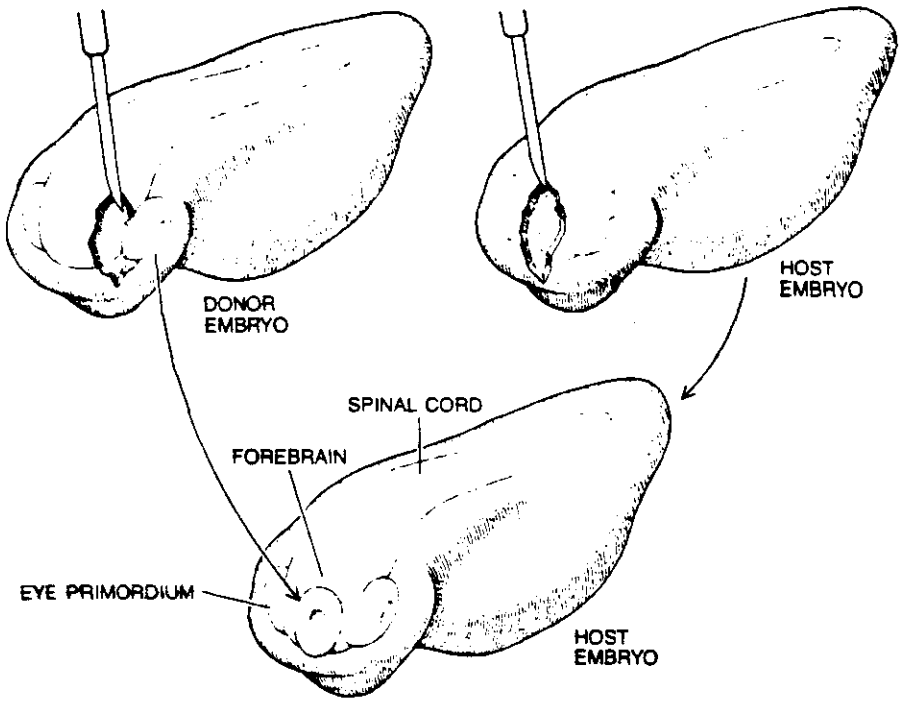
In one series of experiments we re-



ABNORMAL STRIPES in the brain of the leopard frog (*Rana pipiens*) strikingly resemble the stripes in the brain of a mammal. Here the stripes are revealed by injecting the enzyme horseradish peroxidase into one of the animal's optic nerves so that the enzyme is transported into the brain by the axons making up the nerve. The brain is then treated so that the enzyme produces a brown reaction product inside the terminals of the axons. The photograph at the top shows part of the brain of a normal frog. The view is from above. Each large lobe is an optic tectum, the brain region whose cells receive the optic nerve from the eye on the opposite side of the head. The optic nerve from the left eye has been injected with the enzyme; thus the tectum on the right is marked with reaction product. The even tone of brown suggests that the axons projecting to the tectum distribute their terminals there continuously. In this way the tectal cells embody a topographic map of the retina and therefore a map of the visual world. The photograph at the bottom shows the brain of an abnormal frog, one that developed with three eyes because the authors grafted a supernumerary eye primordium (a prospective eye) into the embryo. In this frog axons from the supernumerary eye compete with axons from a normal eye in establishing terminals in the tectum on the left. The supernumerary axons have been injected with the enzyme; they can be seen in the tectum, where their terminals are in stripelike regions. The stripes alternate with stripes of the terminals of axons from the normal eye. Each stripe is about 200 micrometers wide.

moved an eye primordium (the tissue that becomes an eye) from young embryos at a time when the eye was merely an outpouching of the embryonic central nervous system. We then transplanted the primordium into a second embryo in the region of its own two primordia. The embryos we treated in this way became tadpoles and then young frogs with three quite normal eyes. The supernumerary eye usually ended up in front of one of the normal eyes. Sometimes it was at the end of the nose or on top of the head.

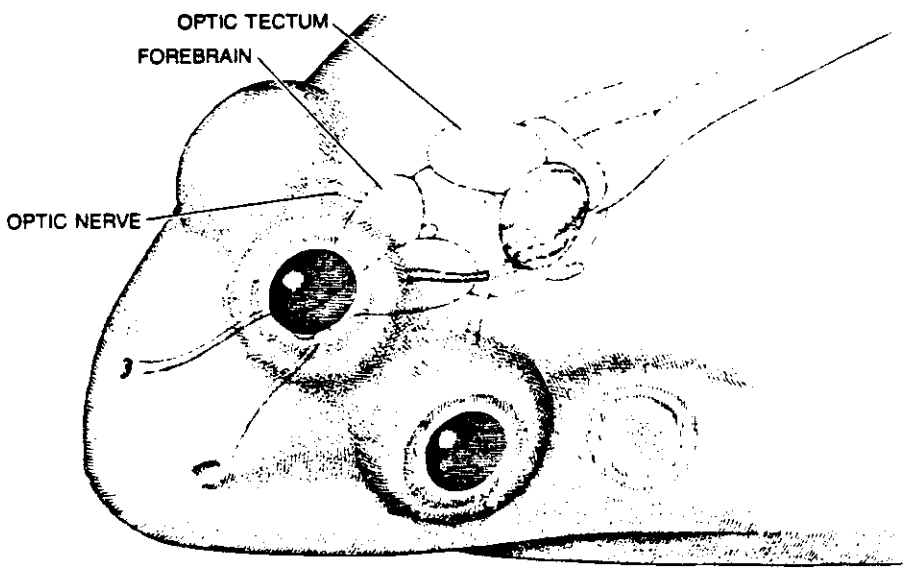
Leopard frogs rely heavily on vision, but unlike cats or monkeys their brains have not evolved the elaborate visual cortex that is characteristic of mammals. Instead the major area for the processing of visual information is in the optic tecta, a symmetrical pair of lobes that occupies much of the midbrain. Each optic tectum receives almost all its retinal axons from only one eye, the contralateral one (the eye on the opposite side of the animal's head). The projection from this eye creates a highly ordered map of the retinal surface, but since the tectum gets no massive projection from the second retina, there are no stripes representing each eye.



SURGICAL PROCEDURE that produces a three-eyed frog requires that an eye primordium be taken from one frog embryo and introduced into a second embryo after tissue has been removed to make room for it. At the time of the transplantation each embryo is some three millimeters long and each eye primordium is an outpouching from the developing forebrain.

The three-eyed frogs are different. In most of them the retina of the supernumerary eye sends axons predominantly to one optic tectum or the other. There the supernumerary axons compete with the normal input to the tectum: the axons arriving from one of the frog's normal eyes. We examined the brain of the three-eyed frogs by injecting radioactively labeled amino acids into either the normal eye or the supernumerary one and waiting a day or two for the isotope to be transported down the axons to their synaptic terminals in the tectum. The tectal lobes of these animals were then sliced and the slices were treated to reveal the distribution of labeled synaptic terminals.

The two sets of terminals (labeled and unlabeled) never mixed in a slice. Instead they were segregated into eye-specific zones that interdigitated periodically. Moreover, a tracing of the zones of labeled terminals through successive slices showed that the zones were aligned into stripes. Each stripe was about 200 micrometers wide and ran roughly from the front to the back of each lobe in a zebralike pattern. The pattern was always similar. It made no difference whether the supernumerary eye came originally from the right or the left side of a donor embryo or whether the axons from the supernumerary eye grew into the right or the left optic tectum. The trajectory taken by the supernumerary axons, the way they bundled together as they grew and the direction from which they entered the tectal lobe also made no difference.



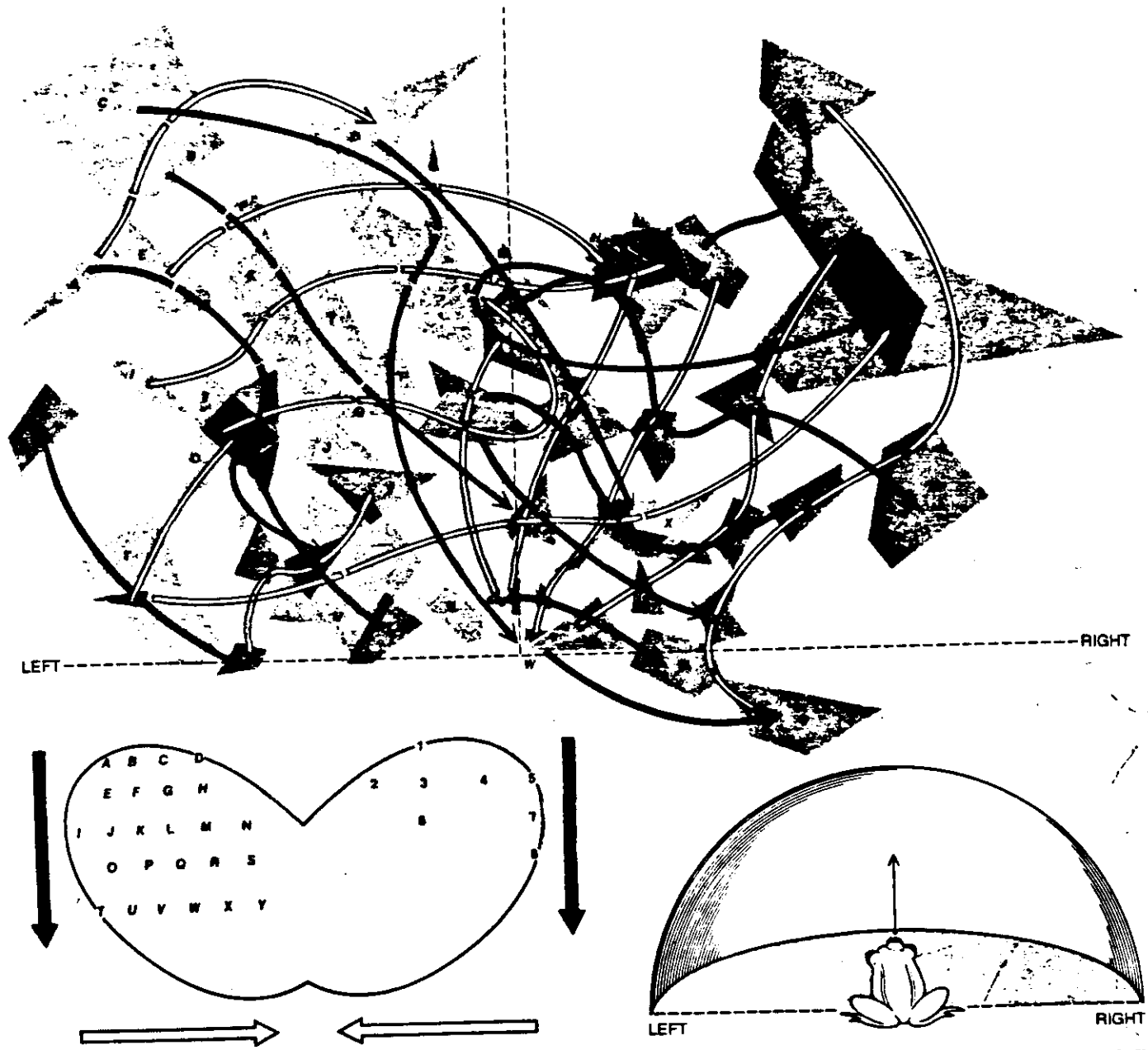
MATURE THREE-EYED FROG has two normal eyes positioned correctly on its head and a third eye either in front of a normal eye or on top of the head. In about three-fourths of all cases the third eye competes with a normal eye to establish axon terminals in one tectum.

In a related experiment several laboratories as well as our own removed one of the two tectal lobes from a normal frog or a goldfish. The axons from the retina that had projected to the missing lobe regenerated. They grew into the remaining tectum, where they competed with the projection already there and produced alternating stripes of terminals arising from axons of the left and the right eye. The experimental doubling of visual input to a tectal region that usually supports only one map of the retina seems inevitably to produce in a lower vertebrate animal a set of complex functional subdivisions that are strikingly similar to the pattern in the visual cortex of normal mammals.

In some of our three-eyed frogs we recorded the activity at the terminals of retinal axons in the tectum while we flashed spots of light on a screen in front of the frog. First we covered the normal eyes and then the supernumerary eye. In this way we could show that each eye's representation on the doubly innervat-

ed tectum was properly aligned with respect to the original axes of the eye in the embryo. Thus the axons in each projection maintained in the tectum a map of the retina from which they arose even though the map is interrupted by the interdigitating stripes. Here again the abnormal frogs resemble the normal mammal. Two retinal inputs produce two separate representations of the visual world in a single target structure.

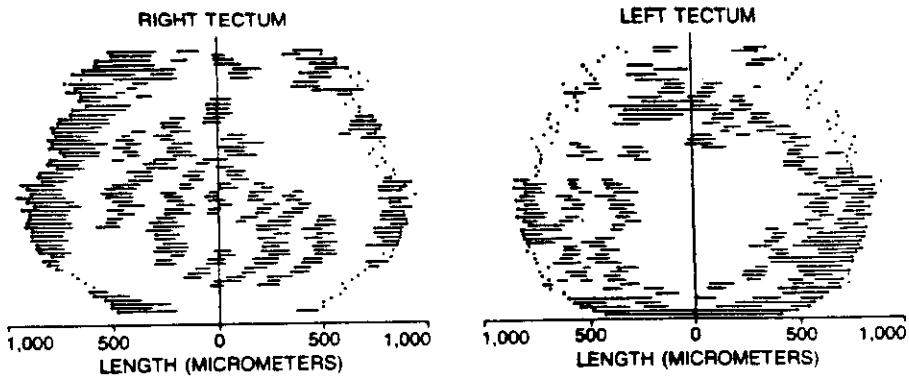
In a mammal, however, the two eyes are symmetrically positioned on the head. This is not the case in a three-eyed frog, where the supernumerary eye is positioned abnormally on the head. In a three-eyed frog the projection from the supernumerary retina to the tectum generally transmits a view of the animal's surroundings that is improperly matched to the view from the normal retina. This means that neurons near each other but in adjacent stripes in the tectum get information about unrelated parts of visual space. The situation could be simulated by fitting one of your own eyes with a prism that bent the light to that eye by, say, 90 degrees. As you looked around, the prism would transmit images from the sky above you into one eye while the other eye saw the terrain in front of you. Both images would be signaled simultaneously



ORIENTATION OF MAPS in the tectal lobes of a three-eyed frog is determined by recording the electrical activity of groups of retinal axons terminating at various places in each tectum as lights are flashed at various places on a hemispherical surface in front of the frog. The numbers *1* through *8* mark sites at which recordings were made in the tectum on the right side of the brain. They also mark receptive fields: the part of the visual world that the cells encountered at each site are found to monitor. In this case the tectum on the right side of the brain embodies a map of the world seen through the eye on the left side of the head (*gray*). Open arrows in the map link directions in the visual world monitored by axon terminals arrayed from side to side in the tectum; closed arrows link directions monitored by axon terminals arrayed from front to back. The letters *A* through *Y* mark sites of recording in the tectum on the left side of the brain. They also mark receptive fields. The tectum on the left side turns out to embody two maps, that of the normal right eye (*black*) and that of the supernumerary eye (*color*). At most recording sites the axon terminals representing each eye are close enough to be detected by a single recording electrode. Both maps are well organized in that when one of the two eyes is covered, the activity of cells in a succession of sites in the tectum can be elicited by stimuli in a succession of parts of the visual world. Yet the normal map and the supernumerary map are not in register: when the animal has both eyes open, neighboring groups of tectal cells may respond to quite different parts of the world.

to the same part of the visual cortex. The world would make little sense.

A three-eyed frog presented with an erratically moving object that mimics its prey (a flying insect) often remains immobile. Occasionally it strikes aberrantly at the stimulus. If the frog is allowed to see through its normal eyes but not the supernumerary one, the strikes are accurate. Presumably the tectal maps representing the normal eyes are correctly aligned with the motor pathways in the nervous system that control the frog's behavior. If the frog is allowed to see through only the supernumerary eye, the strikes are always misdirected. The motor pathways driven by the misaligned visual map move the animal's body in directions that are inappropriate to the prey's position in space.



MIRROR-SYMMETRICAL PATTERNS of stripes are found in a three-eyed frog in which the supernumerary eye sent axons to both optic tecta. Specifically, a hole in the pattern of stripes in one tectum corresponds to a mirror-symmetrical patch of stripes in the other. The patterns suggest that axons from the supernumerary eye compete in the tectum with axons from a normal eye only at particular parts of the tectum determined by where the axons arise in the retina. The surface of each tectum was reconstructed in the illustration by measuring the widths of the stripes in a series of sections of the tectum made at intervals of 20 micrometers.

Questions about the functional or evolutionary significance of stripes in the brain of three-eyed frogs are clearly irrelevant. The third eye is abnormal, and in the absence of substantial input from both of the normal eyes to a single optic tectum the normal frog would get no benefit from a mechanism that evolved specifically to segregate tectal inputs into stripes. On the other hand, the survival of free-living frogs, and in particular their ability to catch the insects on which they feed, depends critically on a robust mechanism to ensure that a precise map of the contralateral retinal surface develops in each tectum.

We began, therefore, to consider the possibility that stripes might arise from the same developmental mechanism that generates maps. Such a link was first suggested as early as 1975 by Simon LeVay, working in collaboration with Hubel and Wiesel at the Harvard Medical School. LeVay proposed that the functional stripes in the visual cortex of the monkey might represent a compromise between two conflicting tendencies: a spreading process in which the axons carrying information from each of the retinas try to fill the entire visual cortex with a map, and a grouping process in which the axons carrying information from each of the retinas try to remain together, as if they were repelled by the inputs from the other eye. The most likely result of the two conflicting tendencies would be interdigitated stripes because a striped configuration would simultaneously optimize both processes.

What, then, are the mechanisms that give rise to neural maps? How could these mechanisms give rise to stripes when two populations of axons map themselves in a [illegible] target zone? Fortunately the projections from the retina to the optic tectum of lower vertebrate animals have long been the subject of studies of neural mapping. R. W. Sperry of the California Institute of Technology was one of the first investigators. Sperry surgically rotated the eyes of newts 180 degrees. In some of the animals he left the optic nerves intact; in others he severed the optic nerves and allowed them to regenerate. In either case the newts made errors of 180 degrees when they snapped at stimuli, and the errors did not improve as time passed. The animals behaved as if they were unaware that their retinas had been rotated. Evidently each part of the retina continued to project its axons to a particular part of the tectum, in spite of the fact that Sperry had intervened so that each part of the retina now monitored abnormal parts of the visual world. Numerous later studies expanded on Sperry's work to show that the part of the tectum that will be innervated by a particular part of the retina is determined in the embryo even before the axons leave the retina and grow into the developing brain.

In 1963 Sperry proposed a theory to explain the consistent alignment of visual maps in the brain. He suggested that retinal cells and tectal cells develop in ways that depend on their position along each of two axes in the retina and the tectum respectively, so that each cell comes to have on its surface a unique set of marker molecules. Axons from the retinal cells can then synapse only with the tectal cells that bear the complementary markers. In short, Sperry visualized a rather rigid chemical-affinity matching between the retina and the tectum. The matching, however, cannot be absolute. Experiments on fishes and amphibians in several laboratories have shown that under some conditions retinal axons synapse with tectal neurons that are not their normal targets. A retina reduced to half its size by surgery can send its axons to form an expanded projection across an entire tectal lobe. Conversely, the axons from an entire retina can compress their map so that it will occupy a surgically created half tectum.

Clearly a mechanism based on a rigid matching of fixed markers on retinal and tectal cells cannot account for the plasticity indicated when the sizes of the retinal and tectal cell populations are surgically altered. Instead the positions of retinal axons in the tectum must be controlled by some mechanism that can adjust to changes in the relative numbers of retinal and tectal cells.

How is the adjustment accomplished? Three possibilities have been formulated. First, the rigid chemoaffinity markers proposed by Sperry could be capable of "respecification," so that surgical perturbation could cause the marker in the retina or the tectum to change. Second, instead of depending on many different markers the identification of cells in the retina or the tectum could depend on gradients of two marker substances, one along each of two axes.

The third possibility is that the retina and the tectum have no markers at all. Instead the axons projecting from the retina to the tectum might maintain their relative order by a cohesion they maintain among themselves as they grow toward the tectum. One must then explain how the map as a whole comes always to have the same orientation in the tectum. In particular the retinal maps in all nonmammalian vertebrate animals represent the central part of the animal's visual world in the anterior (forward) part of the tectal lobe and the more lateral parts of the visual world in the posterior parts of the lobe.

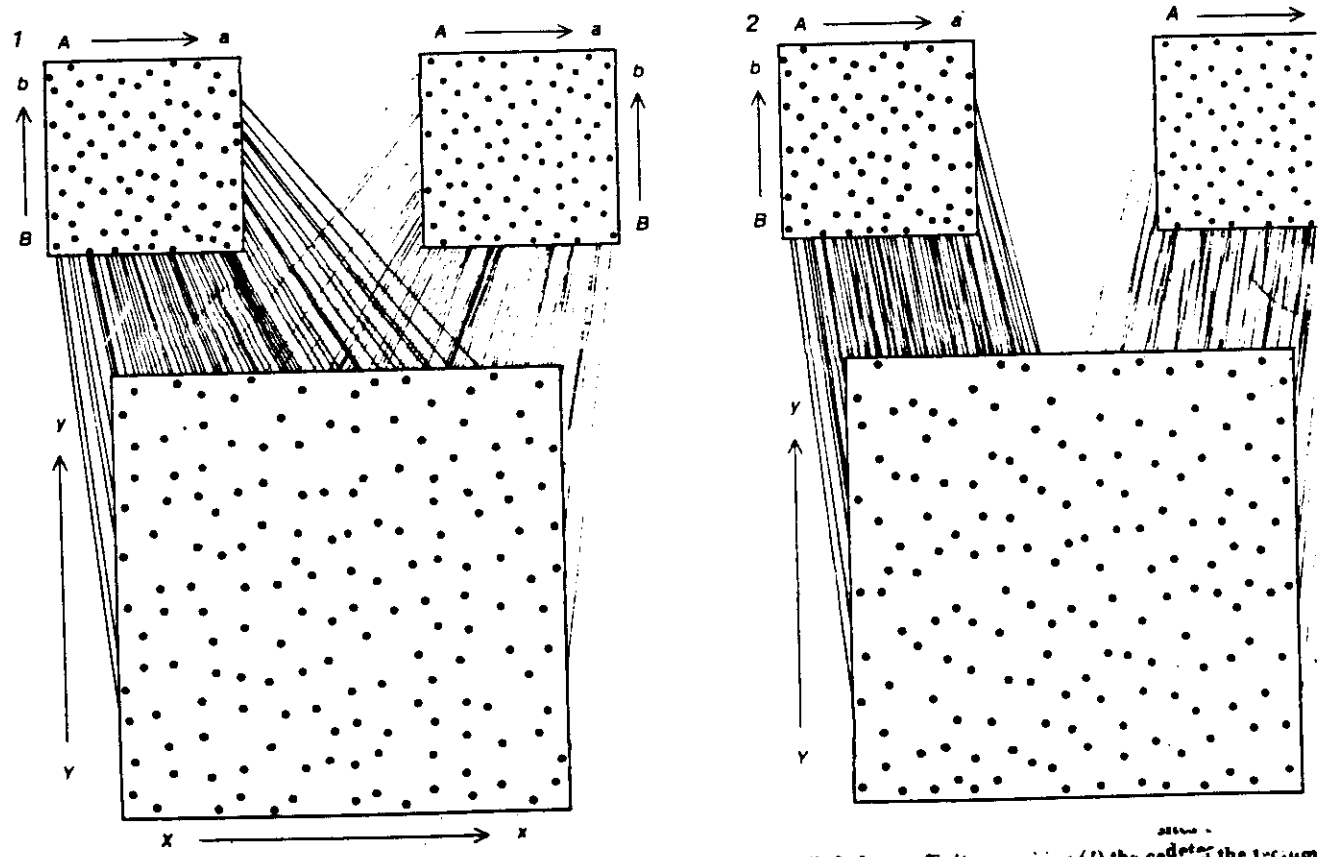
Several lines of evidence are now available to help in evaluating these various possibilities. Indeed, the first possibility, the idea of changing or respecifying rigid retinal or tectal markers, may not be apt. For one thing a series of surgical manipulations done on goldfish in a number of laboratories has shown that a tectum can sequentially receive input from a normal retina, then from an ex-

panded half retina, then from a normal retina again. In addition there are a few reports of experiments on frogs of the genus *Xenopus* in which a region of tectum (although possibly not the same tectal cells) simultaneously receives input from the embryonically anterior half of one retina and the embryonically posterior half of the other retina. Thus if tectal labels respecify, they are capable of doing so frequently. Moreover, the cells within a small region of the tectum can change their labels independently of their neighbors. The tectal markers must be so plastic that they could not identify a cell by its tectal position.

For their part, the markers in the retina, if they exist at all, do not seem to change. Scott E. Fraser, working at Johns Hopkins University, removed an eye from tadpoles of the frog *Xenopus*. The intact eye then projected axons to the contralateral tectum just as it would have done normally. In addition the ventral (lower) part of the intact eye, whose contribution to the optic nerve was still developing at the time of the surgery, sent axons to the full extent of the ipsilateral tectum, the one that would have been innervated by the eye that had been removed. If a ventral region of a retina can project an expanded map to one tectum and a normal map to the other, it must connect to cells in different tectal positions. This makes it unlikely that the expansion of a map involves the respecification of retinal markers.

The second possibility, that of graded markers in the retina and the tectum, accounts for expansions or compressions of a map. It accounts for the ability of cells in a given region of the tectum to receive axons from different parts of a retina. It also accounts for the ease with which a part of a retina can send axons to quite different parts of two tectal lobes. A separate gradient of a marker molecule along each of two axes is sufficient to provide each retinal and tectal position with a unique combination of markers, and the match between retinal and tectal positions is able to adjust to the range of the markers present in the retina or the tectum.

The hypothesis of graded markers predicts, however, that the orientation of a retina's projection on the tectum is maintained after any perturbation. A few experiments show otherwise. Ronald L. Meyer, working at the California Institute of Technology, remc half of a goldfish's retina. The rem eliminated the input to half of one te lobe. At the same time Meyer fo half of the axons from the other ey grow into the half-vacant tectum. might predict that the rerouted a would end in the half-vacant tec much as they would end in the tectu which they normally project. In experiment the axons Meyer rero would have ended in the part of half-vacant tectum that retained its nal input. Instead the rerouted a formed a misoriented (in fact inve projection in the vacant half of the Apparently the rerouted axons fron center of the intact eye got as clo their appropriate tectal position as sible. The other rerouted axons, ever, could not preserve both the c nuity and the orientation of their re map because that would have fc them to terminate in the occupied of the tectum. Meyer's study indi that preserving neighborhood rela must be an important tendency can operate independently in for a map. After all, in Meyer's ex ment neighborhood relations were n tained in an inappropriate region o



3 CONCEIVABLE MECHANISMS by which maps in the brain develop are compared. Two retinas are at the top of each part of the illustration. Their cells (*dots*) are assumed to be labeled by gradients in the concentration of two substances (*A*, *B*) on the surface of the cells. A tectum to which the retinas send their axons is at the bottom of each part of the illustration. In the simplest form of the mechanism called chemoaffinity m... ...g (*1*) the ce... ...the tectum sumed to be labeled by gradients (*X*, *Y*) whose complement the retinal markers guides the ingrowing axons. The axons fro eyes mix as they establish terminals in the tectum, a result that er found in three-eyed frogs. In a somewhat different possible anism (*2*) the axons from each retina maintain their spatial o

tum and at the expense of the normal orientation of the map.

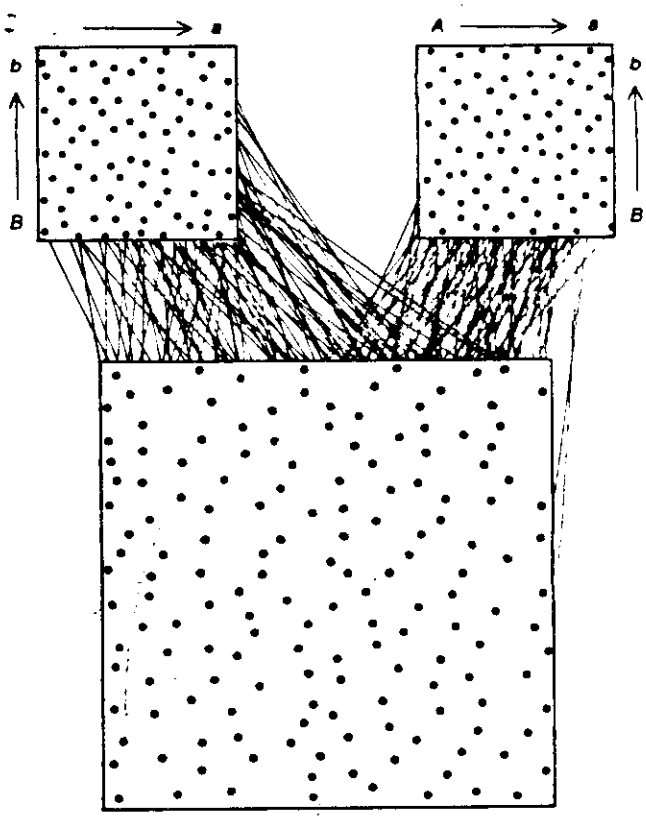
Results of this kind seem to support the third possibility, which favors a cohesion among the axons growing toward the tectum and proposes that there is no chemoaffinity matching between retinal axons and tectal cells. Proponents of the idea cite studies indicating that in fishes, frogs and chickens axons from many (but not all) parts of the retina grow toward the tectum together with axons from cells that are their neighbors in the retina. As we have noted, however, the idea does not explain why normal maps are consistently oriented. The absence of retinal and tectal markers is also difficult to reconcile with a large number of experiments in which retinal axons disrupt the continuity of their map to terminate appropriately in a piece of tectal tissue that is rotated or transplanted to an abnormal position in the tectum.

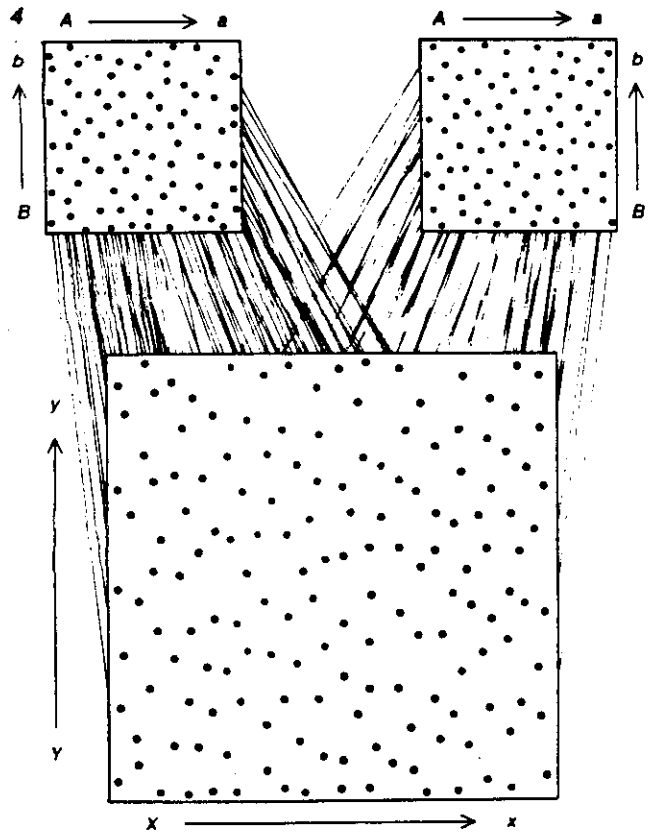
What most convinced us that retinal and tectal markers must exist was a finding we made in three-eyed frogs. In about a fourth of the frogs the supernumerary retina sent axons to both sides of the brain, so that neither tectum was completely striped. In such frogs a hole in the banding pattern in one tectum turned out to correspond to a patch of bands at the mirror-symmetrical location in the other tectum. If ingrowing axons from a third eye simply preserve the topology of the retina, the projections to the tecta should have expanded and formed stripes throughout both lobes. Apparently, however, the supernumerary axons can compete with the axons from the normal retina for tectal space only at locations that are appropriate for the part of the retina in which the axons arise. It seems, therefore, that tectal cells are marked and that retinal axons can discriminate between the tectal labels.

Moreover, recent work in our laboratory shows that a tectum never innervated by a retina can nonetheless develop a map. We removed both eye primordia from frog embryos well before they had begun to send axons into the brain. Later we traced the axonal projections by which the tecta had established maps in other parts of the brain. The maps were identical in eyeless and normal frogs. Thus tectal cells are able to express their positional identities independently of their connections with the retina. Clearly some form of information must be available in the tectum to ensure the proper registration of the retinal map with other visual maps in the brain.

It now seems plain that no one simple mapping mechanism will resolve the controversies that emerge from the many experimental observations. On the one hand it appears that the axons from a certain part of the eye are able to seek out a certain part of the tectum. On the other hand a number of studies (and indeed the stripes in the doubly innervated optic tectum of three-eyed frogs) reflect a cohesiveness among the synaptic terminals representing one retina that cannot be explained by any chemoaffinity matching of retina to tectum.

If one assumes, however, that two independent mechanisms operate in the establishment of neural maps, many of the controversies disappear. Moreover, striping becomes a logical extension of mapping. Suppose that early in the development of a map chemoaffinities graded along at least two axes of the retina and the tectum guide ingrowing axons. The guidance need not be precise: the gradients could be shallow and the affinities could be quite weak. In the visual system of the leopard frog one need only assume that each axon arrives





they grow toward the tectum. The tectum itself provides only enough information (in this case a single gradient) to orient the map. Each retina innervates a separate district of the tectum, a result that is actually never found. In a further possible mechanism (3) the axons maintain their order but get no information from the tectum. In this instance they produce rotated maps. That too is never found. In still another possible mechanism (4) two processes operate. First an imprecise chemoaffinity matching spreads terminals over the tectum in proper orientation. Then a set of local interactions maintains as neighbors in the tectum only the terminals of axons arising from cells that are neighbors in one of the retinas. Stripes are the result because only stripes simultaneously optimize each of the two processes.

in the appropriate quadrant of the tectum. The precision of the map would result from a second stage of development, in which interactions in the tectum would maintain as neighbors only those axon terminals arising from cells that are neighbors in the retina. The result of this sequence will be the compromise recognized by LeVay, Hubel and Wiesel, in which the target zone of two projections is divided into elongated terminal bands.

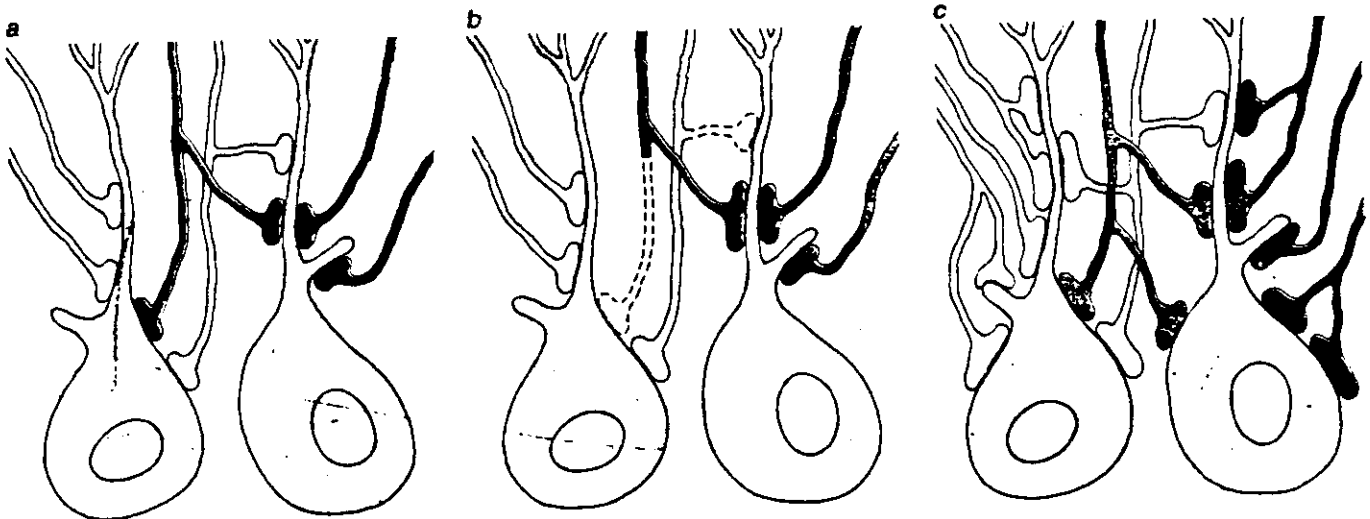
The appeal of chemoaffinity as a hypothesis has inspired investigators to search for marker molecules on the surface of cells in the retina and the tectum. The molecules must be distributed across the retina or the tectum with a gradient and with an ability to bind other substances that could give rise to the known alignment of the tectal map. Several recent advances promise success. For example, workers in the laboratory of Marshall W. Nirenberg at the National Heart, Lung, and Blood Institute expose cells of the immune system of the mouse to extracts of the retina of the chick. The cells in the mouse's spleen that make antibodies are then isolated and cloned. Each resulting cell culture manufactures a highly specific antibody, and one of the antibodies obtained in this way turns out to bind in a graded manner to cells along one axis of the retina. It follows that the unknown molecule to which the antibody is binding has a similar graded distribution. Taking a different experimental approach, Willi Halfter, Michael Claviez and Uli Schwartz of the Max Planck Institute for Viral Research in Tübingen have addressed the question of adhesion between the retina and the tectum. They find that axons from different parts of the chick retina show consistent differences in their ability to bind membranes isolated from chick tectal cells.

Basic questions continue, however, to surround the second stage of mapping: the interactions that keep the terminals from neighboring cells together and presumably give rise to stripes. Michael P. Stryker of the University of California School of *Medicine* in San Francisco has shown that tetrodotoxin, a drug that blocks the ability of neurons to signal one another by means of the voltage spikes called action potentials, prevents or delays the development of stripes in the visual cortex if it is injected into the eyes of a kitten. The projections of the eyes remain mixed in their cortical target zone. N. V. Swindale of the University of Cambridge has reported similar results after raising kittens in the dark.

Apparently neural activity is essential for the cohesiveness among the synaptic terminals that represent one eye or the other. How might this work? Within a given retina neighboring cells that project their axons to the tectum (or toward the visual cortex) tend to generate similar sequences of action potentials because they are connected (by way of intermediate retinal neurons) to many of the same light-receptor cells. Moreover, the correlated action potentials from neurons that are neighbors in the retina are more likely than uncorrelated signals to induce electrical activity in a given tectal cell. Hence well-correlated activity at pairs of synapses could conceivably serve in the tectum (or the visual cortex) to label the synapses from cells that are retinal neighbors. If the tectal neurons were to reinforce synapses from several well-correlated neurons at the expense of synapses whose signaling is relatively ineffective, a roughly topographic map would become precise.

In sum, a two-mechanism model of how the tectal map develops proposes the existence of weak graded affinities that roughly align the retinal axons in the tectum. The map is then precisely ordered by the strengthening of synapses from neighboring retinal cells, which tend to be active simultaneously. Cristoph von der Malsberg and David Willshaw of the Max Planck Institute for Biophysical Chemistry in Göttingen have devised computer simulations in which the selective reinforcement of synapses acts on two roughly topographic projections in a single target zone. They find that the simulations give rise to maps with stripes.

The idea that the efficacy of synaptic terminals can determine their stability and their position in the brain is neither recent nor limited to maps. In the 1940's D. O. Hebb of McGill University suggested that the selective strengthening of synapses might underlie certain aspects of learning. Variants of Hebb's suggestion have since been made to account for the development of neural circuitry in the cerebellum, for the sensitivity of sensory neurons to particular stimuli and for the maturation of the motor connections between the nervous system and the muscles. Although neuroscientists are still far from unraveling the molecular mechanisms that would underlie the selective strengthening or stabilization of synapses, the concept itself is helpful in the effort to understand how neural activity can influence neural structure. Action potentials and the relative effectiveness of synaptic signals are quite likely to be the link between maps and stripes in the brain. They may indeed fine-tune the developing nervous system.



CELLULAR EVENTS thought to underlie the development of a precise tectal map are diagrammed for two cells in a tectum innervated by two eyes. An initial episode of chemoaffinity matching leaves local overlaps in which axons from different eyes impinge on the same tectal cells (*a*). Then the terminals representing one eye are strengthened (in the drawing they are assumed to get bigger) at the expense of terminals representing the other eye (*b*). In addition the density of "correct" terminals could increase (*c*). In either case each retina comes to dominate groups of cells. The terminals representing cells that are neighbors in a retina are likely to transmit well-correlated signals. This correlation could underlie the strengthening of precisely mapped connections and at the same time be responsible for stripes.