Brain Mechanisms of Vision

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A functional architecture that may underlie processing of sensory information in the cortex is revealed by studies of the activity and the organization in space of neurons in the primary visual cortex.

Viewed as a kind of inversion by evolution, the cerebral cortex must be one of the great success stories in the history of living things. Its vertebrates lower than mammals the cerebral cortex is nowhere, if it can be said to exist at all. Suddenly impressive in the lowest mammals, it begins to dominate the brain in carnivores, and it increases explosively in primates; in man it almost completely envelops the rest of the brain, sending to obscure the other parts. The degree to which an animal depends on an organ is an index of the organ's impingement that is even more convincing this size, and dependence on the cortex has increased rapidly as mammals have evolved. A neuron without a cortex appears fairly normal, at least to casual inspection; a man without a cortex is almost a vegetable, speechless, sightless, senseless.

Understanding of this large and indispensable organ is still woefully deficient. This is partly because it is very complex, not only structurally but also in its functions, and partly because neurophysiologists' estimates about the functions have never been wrong. The outlook in changing, however, as techniques improve and as investigators learn how to deal with the huge numbers of intricately connected neurons that are the basic elements of the cortex, with the implications they have for the synapses that connect them. In this article we begin by exploring the basic elements of the cortex, the primary visual cortex (also known as the striate cortex or area 17), the most elementary of the cortical regions concerned with vision. That will necessarily lead us into the related subjects of vision perception, since the workings of an organ cannot easily be separated from its biological purpose.

The cerebral cortex, a highly folded layer of neural tissue about two millimeters thick, is an outermost crust wrapped over the top of, and to some extent tucked under, the cerebrum's hemispheres. In man its total area, if it were spread out, would be about 1.5 square feet. (See a 1974 article in Scientific American on the brain's size in various areas at 20 square feet and was quickly corrected by a neuroanatomist friend in Toronto, who said he thought it was 1.5 square feet, "at least in what Canadian homes"). The folding is presumably mainly the result of such an unlikely structure's having to be packed into a box the size of the skull.

A casual glance at cortical tissue under a microscope shows vast numbers of neurons: about 100 million for each square millimeter of surface, suggesting that the cortex is like a whole has-some 10 billion neurons. The cell bodies are arranged in a few dozen layers that are alternately cell-sparse and cell-rich. In contrast to these marked changes in cell density in successive layers as different depths in the cortex the cells are marked uniformity from place to place in the place of any given layer and in any direction within that plane. The cortex is morphologically rather uniform in two of its dimensions.

One of the first great insights about cortical organization came late in the 19th century. It was gradually realized that this thin rather uniform plan of tissue is subdivided into a number of different regions that have very different functions. The evidence came from clinical, physiological and anatomical sources. It was noted that a brain injury, depending on its location, could cause partial blindness, or blindness or numbness or speech loss, the blindness could be total or limited to half or less of the visual world, and the numbness could involve one limb of the face.

A consistent relation between a given defect and the location of the lesions gradually led to a charting of the most obvious of these specialized regions, the visual, auditory, somatic sensory (body sensation), speech and motor regions.

In many cases a close look with a microscope at cortex stained for cell bodies showed that 1/4 of the relative uniformity there were structural varia-

tions, particularly in the layering pattern, that correlated well with the clinically defined subdivisions. Additional confirmation came from observations or the localities (at the surface of the brain) of the electrical brain waves produced when an animal was stimulated by touching the body, stimulating clicks or tones in the ear or flashing light in the eye. Similarly, motor areas could be mapped by stimulating the cortex electrically and noting what part of the animal's body moved.

This systematic mapping of the cortex has led to a fundamental realization: most of the sensory and motor areas were combined, systematic two-dimensional maps of the world they represent.

Determining a particular small region of cortex could lead to paralysis of one area, or a similar lesion in another small region led to anesthetize one hand or of the upper lip or blindness in one small part of the visual world; if electrodes were placed on an animal's cere-


tex, touching one would produce a corresponding localization of neural activity. Clearly the body was systematically mapped onto the somato-sensory and motor areas; the visual world was mapped onto primary visual cortex, an area on the occipital lobe that is in man and in the macaque monkey (the animal in which our investigations have mostly been conducted) covers about 15 square centimeters.

In the primary visual cortex the map is extraordinarily accurate and distinctive except for the remarkable split of the visual world down the exact middle, with the left half projected to the right cerebral cortex and the right half projected to the left.

The scale of the maps is much more complicated in and perhaps even more complexly understood and is not easily translated. It is nonetheless systematic, and it is similarly crossed, with the right side of the body projecting to the left hemisphere and the left side projecting to the right hemisphere. It is worth remarking that no one has the remaining idea why there should be this neuroanatomical tendency for nervous pathway diagrams to cross.

An important feature of cortical maps in this territory. The scale of the maps varies as it does in a Mercator projection, the rule for the cortex being that
Ocular-dominance columns, one of the two major systems that characterize the functional architecture of the primary visual cortex, are revealed in a periodic bright pattern in this dark-field autoradiograph of a section of a 2-week monkey cortex. The columns extend tangentially across the cortex. Even local in some section, in a brain slice cut perpendicularly to the surface, are regions in which all neurons respond more actively to the right eye than to the left and dark regions separating the bright patches are columns of left-eye preference. The autoradiograph was made by injecting a radioactive labeled amino acid into the right eye of an anesthetized animal. The amino acid was taken up by cells in the retina and transported via the lateral geniculate nucleus, to a layer to the thalamus to cells in the cortex. A brain-slice was reacted with a photographic emulsion, which became exposed for several minutes to and developed exposed about grains overlying the regions of colliculofugal fibers; the light-scattering patches that represent ocular-dominance columns.

Dominance pattern is seen here in an autoradiograph microphotograph of a brain section parallel, rather than perpendicular to the surface of the primary visual cortex. As can be seen in the microphotograph at the top of the page, the label is brightest in one layer of the Griselli cortex, layer IV. This is the level at which the axons bringing visual information to the cortex terminate and where the label therefore accumulates. This section was cut in a plane tangential to the dorsolateral surface of the cortex and just below layer IV, which therefore appears as a ring of roughly parallel bright bands. These are the autoradiographically labeled ocular-dominance regions, which are uninterrupted above instead of edge on. The actual width of the ocular-dominance regions is typically about a millimeter.
the regions of highest discriminative acuteness. In the primary visual cortex an area 17, it is a region of the cerebral cortex: a layered plate of neurons that envelops the primary brain. In the macaque brain, seen here from the side (left) and from above and behind (right), the primary visual cortex (colored area) occupies most of the exposed surface of the two occipital lobes. It also curves around the medial surface below the two cerebral hemispheres. It contains in a complex fold underneath the convex outer surface, as shown in a parasagittal view (top illustration on opposite page) that was cut along the colored line and is viewed in the direction indicated by the arrows.

The primary visual cortex, also known as the striate cortex or area 17, is a region of the cerebral cortex: a layered plate of neurons that envelops the primary brain. In the macaque brain, seen here from the side (left) and from above and behind (right), the primary visual cortex (colored area) occupies most of the exposed surface of the two occipital lobes. It also curves around the medial surface below the two cerebral hemispheres. It contains in a complex fold underneath the convex outer surface, as shown in a parasagittal view (top illustration on opposite page) that was cut along the colored line and is viewed in the direction indicated by the arrows.

The implications of this are far-reaching. Whatever any given region of the cortex does, it does locally. At stages where there is any kind of detailed, systematic topographical mapping the analysis must be piecemeal. For example, in the somatic sensory cortex the messages concerning one finger can be combined and compared with an input from elsewhere on that same finger or with input from a neighboring finger, but they can hardly be combined with the influence from the trunk or from a foot. The same applies to the visual world. Given the detailed order of the input to the primary visual cortex, there is no likelihood that the region will do any thing to correlate information coming in from both far above and far below the horizon, or from both the left and the right part of the visual scene. It follows that this cannot by any stretch of the imagination be the place where actual perception is embodied. Whatever these cortical areas are doing, it must be some kind of local analysis of the sensorimotor world. One can only assume that as the information moves through, a touch or sound is relayed from one cortical area to the next the map becomes progressively more blurred and the information carried more abstract.

Even though the Golgi-method studies of the early 1960's made it clear that the cortex must perform local analyses, it was barely a century before physiologists began with lesser estimates, but, with less power of mapping methods, they have been revising their estimates upward. The important basic notion is that information on any given modality such as sight or sound is transmitted first to a primary cortical area and from there, either directly or via the thalamus, to successions of higher areas. A modern guess is that the number of cortical areas might be between 50 and 100.

The second major insight into cortical organization came from the work of the anatomist Santiago Ramón y Cajal and his pupil Rafael Lorente de Nó. This was the realization that the connections the cortex performs on the information it receives are local. What that means can best be understood by considering the wiring diagram that emerged from the Golgi method used by Cajal and Lorente de Nó. In essence the wiring is simple. Sets of fibers bring information to the cortex; by the time several synapses have been traversed the influence of the input has spread vertically to all cell layers; finally several other sets of fibers carry modified messages out of the area. The detailed connections between inputs and outputs differ from one area to the next, but within a given area they seem to be rather stereotyped. What is common to all regions is the local nature of the wiring. The information carried into the cortex by a single fiber can in principle make itself felt through the entire thickness in about three to four synapses, whereas the lateral spread, produced by branching trees of axons and dendrites, is limited to all practical purposes to a few millimeters, a small proportion of the vast extent of the cortex.
sits and consequent transformations of information are known in any detail. Af-
ter describing the main transformations that take place in the primary visual cor-
texts we shall go on to show how increas-
ing understanding of these cortical func-
tions has revealed an entire world of ar-
chitectural order that is otherwise inac-
tessible to observation.

We can best begin by tracing the vi-
\textit{sual path} in a primate from the 
retina to the cortex. The output from 
each eye is conveyed to the brain by 
about a million nerve fibers bundled 
together in the optic nerve. These fibers 
are the axons of the ganglion cells of the 
retina. The messages from the light-sen-
tive elements, the rods and cones, have 
already traversed from two to four syn-
apses and have involved four other 
types of retinal cells before they arrive 
at the ganglion cells, and a certain 
amount of sophisticated analysis of the 
information has already taken place.

A large fraction of the optic-nerve fi-
bres pass uninterrupted to two rests of 
cells deep in the brain called the lateral 
geniculate nuclei, where they make syn-
apses. The lateral geniculate cells in turn 
send their axons directly to the primary 
visual cortex. From thence, after sev-
eral synapses, the messages are sent to a 
number of further destinations: neigh-
boring cortical areas and also several 
targets deep in the brain. One rea-
ning even projects back to the lateral genicu-
late bodies; the function of this feedback 
path is not known. The main points (or 
the moment is that the primary visual 
cortex is not at an end of the visual path. It is just one stage, probably an 
early one in terms of the degree of ab-
straction of the information it handles.

As a result of the partial crossing of 
the optic nerves is the optic chiasm, the 
geniculate and the cortex on the left side 
are connected to the two left half retinas 
and are therefore concerned with the 
right half of the visual scene, and the 
converse is the case for the right genicu-
late and the right cortex. Each genica-
late and each cortex receives input from 
both eyes, and each is concerned with 
the opposite half of the visual world.

To examine the workings of this visu-
al pathway one strategy since the late 
1950's has been (in principle) simple. 
Beginning, say, with the fibers of the 
opinic nerve, we record with microelec-
trodes from a single nerve fiber and 
try to find out how we can most effectively 
influence the firing by stimulating the 
retina with light. For this one can use 
patterns of light of every conceivable 
size, shape and color, bright on a dark 
background or the reverse, and caution-
ary or moving. It may take a long time, 
but sooner or later we satisfy ourselves 
that we have found the best stimulus for 
the cell being tested, in this case a gangli-
on cell of the retina. Sometimes we are

\begin{quote}
SECTION OF VISUAL CORTEX along the colored line in the illustration on the opposite page was stained by the Nissl method, which makes cell bodies but not fibers visible. The visual cortex is seen to be a continuous layered sheet of neurons about two millimeters thick. The black rectangle outlines a section like the one that is further enlarged in the illustration below.
\end{quote}
We note the result and then go on to another fiber. After studying a few hundred cells we may find that new types become rare. Satisfied that we know roughly how the neurons at this stage work, we proceed to the next stage (in this case the geniculata) and repeat the process. Comparison of the two sets of results can tell us something about what the geniculata does. Then we go on to the next stage, the primary cortex, and repeat the procedure.

Working in this way, one finds that both a retinal ganglion cell and a geniculate cell respond best to a roughly circular spot of light of a particular size in a particular part of the visual field. The size is critical because each cell's receptive field (the patch of retinal receptor cells supplying the cell) is divided, with an excitatory center and an inhibitory surround (an "on-center" cell) or exactly the reverse configuration (an "off center" cell). This is the center-surround configuration first described by Stephen W. Kuffler at the Johns Hopkins University School of Medicine in 1953. A spot exactly filling the center of an on-center cell is therefore a more effective stimulus than a larger spot that invades the inhibitory area, or than diffuse light. A line stimulus (a bar of light) is effective if it covers a large part of the center region and only a small part of the surround. Because these cells have circular symmetry they respond well to such a line stimulus whatever its orientation.

To sum up, the retinal ganglion cells and the cells of the lateral geniculate—the cells supplying the input to the visual cortex—are cells with concentric, center-surround receptive fields. They are primarily conceived not with assessing levels of illumination but rather with making a comparison between the light level in one small area of the visual scene and the average illumination of the immediate surround.

The first of the two major transformations accomplished by the visual cortex is the rearrangement of incoming information so that most of its cells respond not to spots of light but to specifically oriented line segments. There is a wide variety of cell types in the cortex, some simpler and some more complex in their response properties and one soon gains an impression of a kind of hierarchy, with simpler cells feeding more complex ones. In the monkey, there is first of all a large group of cells that behave (as far as is known) just like geniculate cells: they have circularly symmetrical fields. These cells are all in the lower part of one layer, called layer IV, which is precisely the layer that receives the lion's share of the geniculate input. It makes sense that these least sophisticated cortex cells should be the ones most immediately connected to the input.

Cells outside layer IV all respond best to specifically oriented line segments. A typical cell responds only when light falls in a particular part of the visual world, but illuminating that area diffusely has little effect or none, and small spots of light are not much better. The best response is obtained when a line that has just the right tilt is flashed in the region or, in some cells, is swept across the region. The most effective orientation varies from cell to cell and is usually defined slightly differently so that a change of 10 or 20 degrees clockwise or counterclockwise reduces the response markedly or abolishes it. It is hard to convey the precision of this discrimination. If 10 to 20 degrees sounds like a wide range, one should remember that the angle between 12 o'clock and one o'clock is 30 degrees. A line at 90 degrees to the best orientation almost never evokes any response.

Depending on the particular cell, the stimulus may be a bright line on a dark background or the reverse; or it may be a boundary between light and dark regions. If it is a line, the thickness is likely to be important; increasing it beyond some optimum width reduces the response, just as increasing the diameter of a spot does in the case of ganglion and geniculate cells. Indeed, for a particular part of the visual field the geniculate receptive-field centers and the optimal cortical line widths are comparable.

Neurons with orientation specificity vary in their complexity. The simplest, which we call "simple" cells, behave as though they received their input directly from several hubs with center-surround, circularly symmetrical fields. The type of cell found in layer IV is the response properties of these simple cells, which respond to an optimally oriented line in a narrow or a broad but limited location, can most easily be accounted for by requiring that the constriction of the incoming center-surround fields all be excitatory or all be inhibitory, not that they lie along a straight line. At present we have no direct evidence for this scheme, but it is attractive because of its simplicity and because certain kinds of evidence support it. According to the work of Jennifer S. Lund of the University of Washington School of Medicine, who in the past few years has done more than anyone else to advance the understanding of the anatomy of this cortical area, the cells in layer IV project to the layers just above, which is roughly where the simple cells are found.

The second major group of orientation-specific neurons are the far more numerous "complex" cells. They come in a number of subcategories, but their main feature is that they are less particular about the exact position of a line.
Complex cells behave as though they received their input from a number of simple cells, all with the same receptive-field orientation but differing slightly in the exact location of their fields. This scheme readily explains the strong steady firing evoked in a complex cell as a line is kept in the optimal orientation and is swept across the receptive field. With the line optimally oriented, many cells prefer one direction of movement to the opposite direction. Several possible circuits have been proposed to explain this behavior, but the exact mechanism is still not known.

Although there is no direct evidence that orientation-sensitive cells have anything to do with visual perception, it is certainly tempting to think they represent some early stage in the brain's analysis of visual forms. It is worth asking which cells at this early stage would be expected to turn on by some very simple visual form, say a dark blob on a light background. Any cell whose receptive field is entirely inside or outside the boundaries of such an image will be completely unaffected by the image's presence because cortical cells effectively ignore diffuse changes in the illumination of their entire receptive field.

The only cells to be affected will be those whose field is cut by the borders. For the circularly symmetrical cells the ones most strongly influenced will be those whose center is guided by a boundary (because for them the excitatory and inhibitory subdivisions are not equally illuminated). For the orientation-specific cells the only ones to be activated will be those whose optimal orientation happens to coincide with the prevailing direction of the border. And among these the simple cells will be much more exciting than the complex ones, responding optimally only when the border falls along a line separating an excitation and an inhibition region. It is important to realize that this part of the cortex is operating only locally, on bits of the form; how the entire form is analyzed or handled by the brain—how this information is worked on and synthesized at later stages, if useful it is—is still not known.

The second major function of the monkey visual cortex is to combine the inputs from the two eyes. In the lateral geniculate nucleus a neuron may re-
If one maps the right-eye and left-eye receptive fields of a binocular cell by stimulating, first through one eye and then through the other and compares the two fields, the fields turn out to have identical positions, levels of complexity, orientation and directional preference; everything one learns about the cell by stimulating one eye is confirmed through the other eye. There is only one exception: if first one eye and then the other are tested with identical stimuli, the two responses are usually not quantitatively identical, in many cases one eye is dominant, consistently producing a higher frequency of firing than the other eye.

From cell to cell all degrees of occipital dominance can be found, from complete monopoly by one eye through equality to exclusive control by the other eye. In the monkey the cells with a marked eye preference are somewhat commoner than the cells in which the two eyes make about equal contributions. Apparently a binocular cell in the primary visual cortex has connections to the two eyes that are qualitatively identical, but the density of the two sets of connections is not necessarily the same.

It is remarkable enough that the elaborative sets of wiring that produce specificity of orientation and of direction of movement and other special properties should be present in two duplicate copies. It is perhaps even more surprising that these two pools of thalamogenic cells (even in the newborn animal. The wiring is mostly innate, and it presumably is genetically determined. (In one particular respect, however, some manifestation of binocular wiring does take place mostly after birth.)

We now turn to a consideration of the way these cells are grouped in the cortex. Are cells with similar characteristics—complexity, receptive-field position, orientation and ocular dominance—grouped together or scattered at random? From the description so far it will be obvious that cells of like complexity tend to be grouped in layers, with the binocular and monocular cells low in layer IV, the simple cells just above them and the complex cells in layers II, III, and V. Complex cells can further be subcategorized, and the ones found in each layer are in a number of ways very different.

These differences from layer to layer take on added interest in view of the important discovery, confirmed by several physiologists and anatomists during the past few decades, that fibers projecting from particular layers of the cortex have particular destinations. For example, in the visual cortex the deepest layer, layer VI, projects mainly (perhaps only) to the lateral geniculate body; layer V projects to the superior colliculus, a visual station in the midbrain; layers II and III send their projections to other parts of the cortex. This relation between layer and projection site probably deserves to be ranked as a third major insight into cortical organization.

The next stimulus variable to be considered is the position of the receptive field in the visual field. In describing the lateral geniculate nucleus we pointed out that in each layer the opposite half of the visual field forms an ordered topographical map. In the projection from lateral geniculate toprimary visual cortex this order is preserved, producing a cortical map of the visual field. Given this organized map it is not surprising that neighboring cells in this part of the cortex always have receptive fields that are close together, usually, in fact, they overlap. If one plunges a microelectrode into the cortex at a right angle to the surface and records from cell after cell (as many as 100 or 200 of them) in successively deeper layers, again the receptive fields mostly overlap, with each new field bracketed on all the others. The extent of the entire pile of fields is usually less than the size of any one typical field.

There is some variation in the size of these receptive fields. Some of the variation is tied to the layering: the largest fields in any penetration tend to be in

**POSITIONS OF RECEPTIVE FIELDS (numbered from 1 to 9) of cortical neurons mapped by an electronic joystick (at roughly a right angle to the surface are essentially the same (right), although the fields are all eccentric and there is some scatter. In an oblique presentation (right), two to four cells were recorded, at 1.2 millimeter intervals; at each of four sites (numbered from 1 to 4 and one millimeter apart. Each group includes various sizes and some scatter, but now there is also a systematic drift. Since each successive group of cells are somewhat displaced.**
ORIENTATION PREFERENCES of 23 neurons encountered as a microelectrode penetrated the cortex obliquely are charted (left), the most effective tilt of the stimulus changed steadily in a counterclockwise direction. The results of a similar experiment are plotted (center); in this case, however, there were several reversals in direction of rotation. The results of a large number of such experiments, together with the observation that a microelectrode penetrating the cortex perpendicularly encounters only cells that prefer the same orientation (apart from the circulary symmetrical cells in layer IV, which have no preferred orientation) suggested that the cortex is subdivided into roughly parallel bands of neurons, with each slab, called an orientation column, containing neurons with the same orientation specificity (right).

ORIENTATION COLUMNS are visualized as anatomical structures in a dyesoxylme autoradiograph made by the authors and Michael P. Smykai. Radioactively labeled dyesoxylme was injected into a monkey; it was taken up primarily by active neurons, and an early metabolite accumulated in the cells. Immediately after the injection the animal was stimulated with a pattern of vertical stripes, so that cells responding to vertical lines were most active and became most radioactive. In this section perpendicular to surface active-cell regions are narrow bands about 0.5 millimeter apart. Layer IV (with no orientation preference) is, as expected, uniformly radioactive.

ORIENTATION PATTERN, seen face on, is unexpectedly complex. This dyesoxylme autoradiograph is of a section tangential to the somatotopic curved layers of the cortex. The dyesoxylme repre-sent continuously labeled layer IV. In the other layers the orientation regions are intricately curved bands, something like the walls of a maze seen from above, but distance from one band to next is uniform.
where a block of cortex about one or two millimeters in size is what is needed to control the movement of the visual world equivalent to the size of an aggregate field.

These observations suggest the way the visual cortex solves a basic problem: how to analyze the visual scene in detail in the central part and much more crudely in the periphery. In the retina, which has the same problem, for obvious optical reasons the number of millimeters corresponding to a degree of visual field is constant. The retina handles the central area in great detail by having huge numbers of ganglion cells, each subserving a tiny area of central visual field, the layer of ganglion cells in the central part of the retina is thin, whereas as in the outlying parts of the retina it is very thin. The cortex, in contrast, seems to want to be uniform in thickness everywhere. Here there are none of the optical constraints imposed on the retina, and so area is simply allotted in amounts corresponding to the problem at hand.

The machinery in any square millimeter of cortex is presumably about the same as in any other. A few thousand ganglion fibers enter such a region, the cortex does its thing and perhaps 50,000 fibers leave—whether a small part of the visual world is represented in great detail or a larger part in correspondingly less detail. The capacity of the cortex it is suggested, as we indicated at the outset, by the appearance of stained sections. It is compellingly confirmed when we examine the architecture further, looking specifically at its orientation and at ocular dominance.

For orientation we inquire about groupings of cells just as we did with field position, looking first at two cells sitting side by side. Two such cells almost invariably have the same optimal stimulus orientation. If the electrode is inserted in a direction perpendicular to the surface, all the cells along the path of penetration have identical or almost identical orientations (except for the cells deep in layer IV, which have no optimal orientation at all). In two perpendicular penetrations a millimeter or so apart, however, the two orientations observed are usually different. The cortex must therefore be subdivided by some kind of vertical partitioning into regions of constant receptive-field orientation. When we came on this system almost 20 years ago, it intrigued us because it lined so well with the hysterical scheme we had proposed to explain how complex cells are supplied with their inputs. In these diagrams a vertical line passing through the cortex shows that the columns do indeed have the same optimal orientation of receptive fields for the same part of the visual world and that respond to the same line orientation. It seemed eminently reasonable that strongly inter-

layers III, V and VI. The most important variation, however, is linked to eccentricity, the distance of a cell’s receptive field from the center of gaze. The size of the fields and the extent of the associated scatter in the part of the cortex that maps the center of gaze are tiny compared to the size and amount of scatter in the part that maps the far periphery. We call the cells of superimposed fields that are stopped in a penetration beginning at any point on the cortex the “aggregate field” of that point. The size of the aggregate field is obviously a function of eccentricity.

If the electrode penetrates in an oblique direction, almost parallel to the surface, the scatter in field position from cell to cell is again evident, but now there is superimposed on the scatter a consistent drift in field position, its direction dictated by the topographical map of the visual fields. And an interesting regularity is revealed: it turns out that moving the electrode about one or two millimeters always produces a displacement in visual field that is roughly enough to take one into an entirely new region. The movement in the visual field, in short, is about the same as the size of the aggregate receptive field. For the primary visual cortex this holds wherever the recording is made. At the center of gaze the fields and their associated scatter are tiny, but so is the displacement corresponding to a one-millimeter movement along the cortex. With increasing eccentricity (farther out in the visual field) both the field and scatter and the displacement become larger, in parallel fashion. It seems that every-

GROUPING OF CELLS according to ocular dominance was revealed by physiological studies. In the typical vertical penetrations of the cortex (1) a single electrode encounters only cells that respond preferentially to the left eye (L), and, in layer IV, cells that respond only to the left eye (L), as in another vertical penetrations (2) the cells all have right-eye dominance (R) or, in layer IV, are driven exclusively by the right eye (R). In an oblique penetration (3) there is a regular alternation of dominance by left eye or the other eye. Repeated penetrations suggest that the cortex is subdivided into regions with a cross-sectional width of about 4 millimeters and with axis perpendicular to the cortical surface and layers: the ocular-dominance columns.

LEFT EYE

RIGHT EYE

HORIZONTAL

VERTICAL

HORIZONTAL

VERTICAL

BINOUCULAR CELL in the cortex can be influenced independently by both eyes or more strongly by both eyes together. Here the left-eye and right-eye fields are marked for a complex cell whose receptive field is the upper left quadrant of the visual field. (The lines represent the horizontal and vertical meridians of the field, intersecting at the point of fixation.) The two receptive fields are identical, but the amount of suppression may differ depending on whether the left eye or the right eye is stimulated. Preference for one eye is called ocular dominance.
connected cells should be grouped together.

If the cortex is diced up into small regions, one can see anything more about the three-dimensional shape of the regions than that their walls are perpendicular to the surface? Are neighboring regions related in any systematic way or are they regionally unresponsive to all possible orientations scattered over the cortex at random? We began to study these questions simply by penetrating the cortex obliquely or parallel to the surface. When we did this experiment in about 1965, the result was so surprising that we could hardly believe it. Instead of a random assortment of successive orientations there was an amazing orderliness. Each time the electrode moved forward as little as 12 or 10 micrometers (thousands of a millimeter) the orientation changed by a small step, about 10 degrees on the average; the steps continued in the same direction, clockwise or counterclockwise, through a total angle of anywhere from 90 to 270 degrees. Occasionally such a sequence would reverse direction suddenly, from a clockwise progression to a counterclockwise one or vice versa. These reversals were unpredictable, usually coming after steady progressions of from 90 to 360 degrees.

Since, making this first observation we have seen similar order in almost every monkey. Every movement of the penetration in orientation or, less frequently, there are stretches in which orientation stays constant. The successive changes in orientation are small enough so that it is hard to be sure that the regions of constant orientation are finite in size; it could be that the optimal orientation changes in some sense continuously as the electrode moves along.

We became increasingly interested in the three-dimensional shape of these regional subdivisions. From considerations of geometry alone the existence of small or zero changes in every direction would have been a clear indication that the cells were not oriented. For we would have seen a choroid plexus, a slit-like structure, a column of tissue a few millimeters thick, the axons of which could easily be planar, like slices of bread, seen from above they might well have the form of swirls, which could easily explain the reversals in the direction of orientation changes. Recording large numbers of cells in several parallel electrode penetrations seemed to confirm this prediction, but it was hard to examine more than a tiny region of brain with the microelectrode.

Fortunately an ideal anatomical method was invented at just the right time for us. This was the 2-deoxyglucose technique for assessing brain activity, devised by Louis Sokoloff and his group at the National Institute of Mental Health (see "The Chemistry of the Brain," by Leslie L. Ivens; Scienvoice, Annual Bioprint 1968). The method capitalizes on the fact that brain cells depend mainly on glucose as a source of metabolic energy and that the closely similar compound 2-deoxyglucose can to some extent mislead the cells. If deoxyglucose is injected into an animal, it is taken up actively by neurons as though it were glucose; the more active the neuron, the greater the uptake. But reasons best known to biochemists the sequence stops with a metabolite that cannot cross the cell wall and therefore accumulates within the cell. The Sokoloff procedure is to inject an animal with deoxyglucose that has been labeled with the radioactive isotope carbon-14, stimulate the animal in a way calculated to activate certain neurons.
and then immediately examine the brain for radioactivity, which reveals active areas where cells have taken up more deoxyglucose than those in quiescent areas. The usual way of examining the brain for this purpose is to cut very thin slices of it (as one would for microscopic examination) and press them against a photographic plate sensitive to the radioactive particles. When the film is developed, any areas that were in contact with radioactive material are seen as dark masses of developed silver grains. Together with Michael P. Stryker we adapted the Sokoloff method to our problem, injecting an anesthetized animal with deoxyglucose and then moving a pattern of black and white vertical stripes back and forth 1.5 meters in front of the animal for 45 minutes. We then cut the brain into slices, either perpendicular to the surface of the cortex or parallel to it.

The autoradiographs quickly confirmed the physiological results. Sections cut perpendicular to the surface showed narrow bands of radioactivity about every 570 micrometers (roughly half a millimeter), extending through the full thickness of the cortex. Evidently these were the regions containing cells responsive to vertical lines. The deep parts of layer IV was uniformly radiopaque, as was expected from the fact that the cells in the layer have circularly symmetrical receptive fields and show no orientation selectivity. Sections cut parallel to the surface showed an unexpectedly complex set of periodically spaced bands, often swirling, frequently branching and rejoining, only here and there forming regular parallel slits. What was particularly striking was the uniformity of the distance from one band to the next over the entire cortex. This fitted perfectly with the idea of a uniform cortex. Moreover, the distance between stripes fitted well with the idea that the cortical machinery must repeat itself at least every millimeter. If the distance were, for example, 10 millimeters from vertical through 180 degrees and back to vertical, sizable parts of the visual field would lack cells sensitive to any given orientation, making for a sketchy and extremely bizarre representation of the visual scene.

The final variable whose associated architecture needs to be considered is eye preference. In microelectrode studies neighboring cells proved almost invariably to project the same eye. If in vertical penetrations the first cell we encountered preferred the right eye, then so did all the cells, right down to the bottom of layer IV; if the first cell preferred the left eye, we did all the rest. Any penetration favored one eye or the other with equal probability. Since the cells of layer IV are monocular, there it was a matter not of eye preference but of eye monosity. If the penetration was oblique or horizontal, there was an alternation of left and right preferences, with a rather abrupt switchover about every half millimeter. The cortex thus proved to be sliced up into a second set of regions separated by vertical walls, that extend through the full cortical thickness. The ocular-dominance system was apparently quite independent of the orientation system, because in oblique or tangential penetrations the two sequences had no apparent relation to each other.

The basis of these ocular-dominance columns, as they are to be called, seems to be quite simple. The terminals of geniculate fibers, some subserving the left eye and others the right, group themselves as they enter the cortex so that in layer IV there is no mixing. This produces left-eye and right-eye patches at roughly half-millimeter intervals. A neuron above or below layer IV receives connections from that layer from up to about a millimeter away in every direction. Probably the strongest connections are from the region of layer IV closest to the cell, but it is presumably dominated by whichever eye feeds that region.

Again we were most curious to learn what these left-eye and right-eye regions might look like in three dimensions; any of several geometries could lead to the cross-sectional appearance the physiology suggested. The answer first came from studies with the silver-degeneration method for mapping connections, devised by Walle J. H. Nauta of the Massachusetts Institute of Technology. Since then we have found three other independent anatomical methods for demonstrating these columns:

A particularly effective method (because it enables one to observe in a single animal the arrangement of columns over the entire primary visual cortex) is based on the phenomenon of axonal transport. The procedure is to inject a radioactively labeled amino acid into an area of nerve tissue. A cell body takes up the amino acid, presumably incorporates it into a protein and then transports it along the axon to the terminals. When we injected the material into one eye of a monkey, the retinal ganglion cells took it up and transported it along their axons, the optic nerve fibers. We could then examine the destinations of these fibers in the lateral geniculate nuclei by coating tissue slices with a silver emulsion and developing the emulsion; the radioactive label showed up clearly in

**BLOCK OF CORTEX** above a millimeter square and two millimeters-deep (light color) can be considered an elementary unit of the primary visual cortex. It consists of a set of orientable slabs subserving all orientations and one set of ocular-dominance slabs, subserving both eyes. The pattern is repeated throughout the primary visual area. The pathway of the boundaries at the right eye in the left eye, as a vertical, horizontal or oblique orientation is arbitrary, and represents the slabs on flat planes intersecting at right angles in an over-simplification.
the three complimentary layers of the geniculater on each side.

This method does not ordinarily trace a path from one eye nerve to the next neuron and its termi-
nals, however, and we wanted to follow the path all the way to the cortex. In 1971 Bernice Grafstein of the Cornell University Medical College discovered that after a large enough injection in the eye of a single optic nerve material escaped from the optic-nerve terminals and was taken up by the cells in the geniculater and transported along their axons to the cortex. We had the thought that a similarly large injection in a monkey, combined with autoradiog-
graphy, would reveal the geniculater and optic-nerve terminals from one eye in layer IV of the visual cortex.

Our first attempt yielded disappointingly negative results, with only faint hints of a few silver grains visible in layer IV. It was only after several weeks that we realized that by resorting to dark-field microscopy we could take advantage of the light-scattering properti-
ies of silver grains and we increased the sensitivity of the method. We borrowed a dark-field condenser, and when we looked at our first slide under the mi-
roscope, there shining in all their glory were the pericentric patches of label in layer IV (see fig. Illustration on page 47).

The next step was to try to see the patches with a section parallel to its surface. The monkey cortex is of course shaped, and so a section par-
allel to the surface and tangent to layer IV shows that layer as a circle or an oval, while a section below layer IV shows it as a ring. By assembling a series of such sections, we were able to reconstruct the pattern of projections from the entire ganglion cell complex for the entire primary visual cortex, once more emphasizing the uniformity of the cor-

tex. Again the widths fit perfectly with the idea that all of the apparatus needed to look after an area the size of an aggre-
gate field must be contained within any square millimeter of cortex. The two techiques, deoxyglucose labeling and silver stain transport, have the great ad-
vantage of being mutually compatible, so that we have been able to apply both together, one to mark orientation lines and the other to see the ocular-domi-
nance columns. The number of brains examined so far is too small to justify any final conclusions, but the two sys-
tem appear to be quite independent, neither parallel nor at right angles but intersecting at random.

The function served by ocular-domi-
nance columns is still a mystery. We know there are neurons with all grades of eye preference throughout the entire ganglion 

cal layer of the visual fields, and it seems that there is a regular, patterned system of converging inputs. If it is true, this system will be uniform, with uni-
form eye favored by accident in any one place. Why there should be all these grades of eye preference everywhere is not clear, but our guess is that it has something to do with stereoscopic depth perception.

Given what has been learned about the primary visual cortex, it is clear that one can consider any element of a piece of cortex to be a block about a millimeter square and two millimeters
deep. To know the organization of this chunk of tissue is to know the organiza-
tion for all of area 17; the whole must be easily mapped. An iteration of this ele-
mentary unit. Of course the elementary units should not be thought of as dis-
crete, separable blocks. Whether the area of orientation slants begins with a slant-
representing a vertical orientation, an oblique one or a horizontal one is com-
pletely arbitrary, so too is whether an ocular-dominance sequence begins with a left-plus-right or dominance slant or a right-plus-left pair. The same thing is true for virtually any system of color or-

code or for any other repetitve pattern such as is found in wallpaper.

What, then, does the visual scene really look like as it is projected onto the visual cortex? Suppose an animal fixates its gaze on some point and the only ob-
ject in the visual field is a straight line above and to the left of the point where the gaze is riveted. If such a scene were to light up, and if one could stand above the clefts and look down at it, what would the pattern be? To make the problem more interesting, suppose the pattern is seen by one eye only. In view of the irregularities just described the pattern viewed out to be not a line but merely a set of regularly spaced patches (see illustration above). The reason can be checked directly by exposing a mono-
key with one eye closed to a set of verti-

cal strips and making a deoxyglucose autoradiograph. The autoradiographs should not be a great surprise; it is a set of regularly spaced patches, which sim-
ply represents the intersection of the two sets of column systems. Imagine the surprise and bewilderment of a little green man looking at such a version of the outside world.

Why evolution has gone to the trouble of designing such an elaborate architecture is a question that continues to fascinate us. Perhaps the most plausible notion is that the column systems are a solution to the problem of portraying more than two dimensions on a two-dimensional surface. The cortex is dealing with at least four axes of values: two for the x and y position variables in the visual field, one for orientation and one for the different degrees of eye preference. The two surface coordinates are used up in designating field position; the other two variables are accommodated by digitizing the cortex with subdivisions so fine that one can run through a complete set of orientations or eye preferences and meanwhile have a shift in visual-field position that is small with respect to the resolution in that part of the visual world.

The strategy of subdividing the cortex with small vertical partitions is certainly not limited to the primary visual area. Such subdivisions were first seen in the somatic sensory area by Vernon B. Mountcastle of the Johns Hopkins University School of Medicine about 10 years before our work in the visual area. In the somatic sensory area, as we pointed out above, the basic topography is a map of the opposite half of the body, but superimposed on that is a twofold system of subdivisions, with some areas where neurons respond to the movement of the joints or pressure on the skin and other areas where they respond to touch or the bending of hairs. As in the case of the visual columns, a complete set here (one area for each kind of neuron) occupies a distance of about a millimeter. These subdivisions are analogous to ocular-dominance columns in that they are determined in the first instance by inputs to the cortex (from either the left or the right eye and from either deep receptors or receptors in the upper skin layers) rather than by connections within the cortex, such as those that determine orientation selectivity and the associated system of orientation regions.

The columnar subdivisions associated with the visual and somatic sensory systems are the best-understood ones, but there are indications of similar vertical subdivisions in some other areas: several higher visual areas, sensory parietal regions recently studied by Mountcastle and the auditory region, where Thomas J. Imig, H. O. Adkins and John F. Brugge of the University of Wisconsin Medical School and their colleagues have found subdivisions in which the two ears seem alternately to add their information or to compete.

For most of these physiologically defined systems (except the visual ones) there is as yet no anatomical correlate. On the other hand, in the past few years several anatomists, notably Edward G. Jones of the Washington University School of Medicine and Nauta and Patricia Goldman at M.I.T., have shown that connections from one region of the cortex to another (for example from the somatic sensory area on one side to the corresponding area on the other side) terminate in patches that have a regular periodicity of about a millimeter. Here the columns are evid- ent morphologically, but one has no idea of the physiological interpretation. It is clear, however, that fine periodic subdivisions are a very general feature of the cerebral cortex. Indeed, Mountcastle's original observation of that feature may be said to supply a fourth, profoundly insightful into cortical organization.

I t would surely be wrong to assume that this account of the visual cortex in any way exhausts the subject. Color, movement and stereoscopic depth are probably all dealt with in the cortex, but in what extent or how it is still not clear. There are indications from work we and others have done on depth and on color by Semir Zeki of University College London that higher cortical areas in which the primary area projects directly or indirectly may be specialized to handle these variables, but we are a long way from knowing what the handling involves.

What happens beyond the primary visual area, and how is the information on orientation exploited at a later stage? Is one to imagine ultimately finding a cell that responds specifically to some very particular item? (Usually one's grandmother is selected as the particular item, for reasons that escape us.) Our answer is that we doubt there is such a cell, but we have no good alternative to offer. To speculate broadly on how the brain may work is fortunately not the only course open to investigators. To explore the brain is more fun and seems to be more profitable.

There was a time, not so long ago, when one looked at the millions of neurons in the various layers of the cortex and wondered if anyone would ever have any idea of their function. Did they all work in parallel, like the cells of the liver or the kidney, achieving their objectives by purely bulk, or were they each doing something special? For the visual cortex the answer seems now to be known in broad outline: Particular stimuli activate particular groups of neurons, which do indeed perform particular transformations. It seems reasonable to think that if the secrets of a few regions such as this one can be unlocked, other regions will also in time give up their secrets.