

Early Exploration of the Visual Cortex

Review

David H. Hubel*[‡] and Torsten N. Wiesel[†]

Harvard Medical School
Department of Neurobiology
Boston, Massachusetts 02115
[†]Office of the President
Rockefeller University
New York, New York 10021

Beginnings

Looking back 40 years, it is hard to imagine how the prospects could have been better for us when, in the spring of 1958, we set out to try to understand the visual cortex. We were both medically trained. Torsten had a long experience in psychiatry—he grew up in a mental hospital outside Stockholm and had practiced both adult and child psychiatry before deciding to go back to basics and join the neurophysiology laboratory of C. H. Bernhard, his preclinical professor in the subject. After one year studying epilepsy in cats he was invited to come as a postdoctoral student to Stephen Kuffler's laboratory in the Wilmer Institute at the Johns Hopkins Medical School. There in the mid-50s he collaborated with K. T. Brown in layer-by-layer analysis of the cat intraretinal electroretinogram. David grew up in Montreal, graduated in medicine at McGill, and did a year of neurology residency at the Montreal Neurological Institute followed by a year of clinical EEG with Herbert Jasper. After a further year in neurology at the Johns Hopkins Hospital he began research at the Walter Reed Institute in Washington, D.C., where he set out to develop a method for recording from single cells in the cortex of awake, behaving cats. To do this he had first to devise a lacquer-coated tungsten microelectrode strong enough to penetrate the animal's dura, and to adapt the Davies' closed chamber to chronic recording. Having got the technique working, he decided to begin by recording from the cat's visual cortex.

What brought the two of us together was a lucky fluke. On leaving Walter Reed, David had planned to join Mountcastle's group at Johns Hopkins Medical School, to continue his work on vision there. But in the spring of 1958 the space in physiology was being remodeled, with no prospect of its being ready for occupation for many months. Stephen Kuffler had gotten wind of this, and since Ken Brown had just left he suggested that David work with Torsten for the 9 months or so until the space in physiology was ready. We could never have predicted that what began as a 9-month collaboration would turn out to last 25 years.

We were lucky in many ways. Most important was the incredible stroke of fortune to be in the laboratory of Stephen Kuffler (Figure 1), where three groups worked completely independently, packed into a tiny amount of space, in an informal and friendly atmosphere. Next, only one or two other groups had ever put microelectrodes into the visual cortex, and they had not gotten

much further than obtaining on, off, or on-off responses to diffuse light. Neurophysiology in the late 50s was underpopulated, and CNS studies were mainly concentrated on work in spinal cord. We moved into a vacuum, and had the visual cortex virtually to ourselves for the entire decade of the 60s. Finally, we were just a few buildings away from the world's leading center for single-cell cortical physiology, led by Vernon Mountcastle. There the closed chamber technique had been developed by Davies for cortical recording and the strategy of anatomically reconstructing long electrode tracks had led to Mountcastle's discovery of cortical columns in the somatosensory system. Perhaps because of the influence of Jerzy Rose, this was one of the few places in the world where neurophysiology was closely linked with neuroanatomy. Mountcastle was a frequent visitor to Steve Kuffler's lab, and we also met him a few times a week in the Hopkins doctors' dining room, where people interested in the nervous system usually sat at the same table.

Kuffler's laboratory was in the basement of the old Wilmer Eye Institute, just next to the outpatient eye clinic. It was certainly cozy. Our entire group consisted of Steve, the two of us, Ed Fushpan and David Potter (who had just arrived from the laboratory of Bernard Katz at University College, where they had discovered the electrical synapse), Taro Furukawa (working with Fushpan), and Joseph Dudel (working with Potter and Steve). Steve had a small office just across from our lab, and the rest of the group were packed into three 15 × 15-foot labs.

A few months before we were due to start, in the early spring of 1958, David came over from Washington for the day and the two of us met with Steve Kuffler at the hospital cafeteria. It was clear that our strategy (perhaps too strong a word) should be to extend into the cortex the work Steve had done in the cat retina in the early 1950s. Steve had long since changed his research back to his first love, synaptic transmission, but wished to keep a vision lab going to justify his presence at the Wilmer Ophthalmology Institute. To say that the two of us had been inspired by Steve's first vision papers in the early 50s (*Journal of Neurophysiology*) would clearly be a major understatement. Steve's way had been paved by Adrian, Hartline, Barlow, and others, in invertebrates and lower vertebrates, all involving the use of natural stimuli to activate single cells and map their receptive fields, but his work in cats was much closer to our interests since it was in a higher mammal and had the immediate appeal of explaining why, in the perception of white and black, contrast across borders is so much more important than overall light levels. It also supplied a picture of the output of the retina, even though the receptors and intermediate retinal stages had not yet been studied and would not be for some years.

Clearly the most exciting question we could ask was what the brain did with the information it got from the retina. We were certainly equipped to take it on, given Torsten's familiarity with techniques of stimulating and recording from the retina and with receptive fields of

[‡]To whom correspondence should be addressed.



Figure 1. Stephen Kuffler at a Department Picnic, Boston, Sometime in the Mid-70s

retinal cells, and David's techniques for making stable cortical recordings. For the time being we decided to abandon awake-behaving methods because work with receptive fields required a control of visual stimuli only obtainable with the eyes paralyzed, which in turn meant that animals had to be anesthetized and artificially respirated and the eyes had to be fitted with contact lenses—all methods Steve had worked out in the early 50s. While at Walter Reed, David had managed to record from a few lateral geniculate cells in awake cats and had shown that their receptive fields were center-surround, like the fields of retinal ganglion cells, so it seemed more interesting for the time being to finesse the geniculate and go right to the cortex. Only in the last few years has David been able to return to his initial intention to study single cortical neurons in the awake animal.

Our plans can have taken no more than about 30 minutes to formulate, that day in the Hopkins cafeteria.

The revolution that occurred in cortical physiology in the late 50s and early 60s was to a large extent technical in origin and depended on the microelectrode, the closed chamber's ability to dampen cardiovascular and respiratory pulsations of cortex, and the development of the electronics necessary to work at high gain into high impedances. Before single-cell recording one was dependent on coarse surface electrodes, which could only record synchronous electrical activity. But such activity, in the form of "evoked potentials", had been important as a method for determining the representation of the body in the somatosensory cortex and the visual fields in the visual cortex. In 1941 at the Wilmer, Talbot and Marshall had used evoked potentials to make a topographic map of the striate cortex of the cat and macaque monkey (Talbot and Marshall, 1941), and in 1950 Thompson, Woolsey, and Talbot used the same methods to map visual areas I and II in the rabbit and visual 1 in the macaque monkey (Thompson et al., 1950). The work was extended in a wonderfully imaginative

way in 1961 by Daniel and Whitteridge. They worked out theoretically the three-dimensional shape of the striate cortex by transforming the spherical shape of the retina according to the known variation in magnification factor with distance from the fovea; the predicted result was something resembling a pear in shape, which they went on to verify by modeling a real monkey brain in rubber.

Roughly speaking, this was the background at the beginning of our exploration of the world of single cells in the visual cortex. Our time was limited to less than 1 year, or so it seemed in July, 1958. We had to get started quickly if we were to accomplish anything.

First Recordings

We did our first experiment within a week or so of David's arrival. Everything was makeshift, and we simply dove in. We had no Horsley-Clark stereotaxic apparatus, so at first we held the cat's head in the head-holder part of the ophthalmoscope Kuffler had designed with Talbot (Talbot and Kuffler, 1952), with the cat's head twisted around and looking up towards the ceiling. We could thus stimulate the retina of one eye directly with a light spot which we could observe by looking down through the ophthalmoscope. To make a small spot of light one took a small plate of brass, the size of a microscope slide, into which a small hole had been drilled and placed it into a slot in the ophthalmoscope so that it intercepted the light path. To produce a black spot one used a piece of glass onto which a thin blackened circle of metal had been glued. We could vary spot sizes using about a dozen of these pieces of brass and glass. To record from visual cortex we used the tungsten microelectrode and adapted the hydraulic advancer that had been used for recording from the awake cat.

A few weeks after we started we had our first major break. We had been recording in visual cortex from a large, isolated, and stable cell for several hours without getting anywhere: none of our retinal stimuli produced

any change in the cell's firing. Then we began to sense vague changes in firing as we stimulated one part of the retina. Suddenly there was a vigorous discharge, which occurred as we slid the glass slide into place. It took a while to discover that the firing had nothing to do with turning on or off the dark spot but occurred as we slid the piece of glass into and out of the slot. The stimulus turned out to be the faint but sharp line shadow cast on the retina by the moving edge of the glass. As we played further with the stimulus we could satisfy ourselves that the shadow only evoked responses over a small retinal area and a rather narrow range of orientations, about 30 degrees to either side of a sharply defined optimum. When we finally decided to pull out and go home the cell was still going strong. Nine hours had passed from the time we started recording from it.

It would be easy to think of this early revelation as a piece of extraordinary luck. It would of course have been very bad luck had we quit after 5 hours instead of going on for 9. But we rather think of the discovery as the result of Swedish and Canadian dogged persistence. At the time we wondered if that cell was a bizarre exception, and whether we might never see another one like it. But in the weeks that followed we did indeed see more examples, and soon we began to suspect that orientation selectivity was the rule for cells in area 17 (as the striate cortex [V1] was then known). We had begun with the hope that we might get some understanding of cortical cells by mapping their receptive fields with small spots into separate excitatory and inhibitory areas, as Steve had done. For many of the cells we did obtain clear on and off responses from distinct subdivisions of the receptive fields, but the areas were arranged not as center-surround, in retinal ganglion cell fashion, but typically as a long narrow on region with off regions to either side. This at once explained why the best responses were obtained with straight-line edges or long narrow rectangles. We called such cells "simple". Other cells, including the first, 9-hour one, strongly favored line stimuli but could not be mapped into separate opponent areas. We did not know what to make of these cells and put them to one side, calling them "complex". Within about a month of our first experiment we were ready to sit down and write our first joint paper describing the simple cells.

Vernon Mountcastle must have been mystified if not scandalized when he looked in on us during one of his visits to Steve. We had abandoned the ophthalmoscope in favor of a projection screen but were still using the old head holder, with the cat facing the ceiling. For a screen we had brought in a set of bed sheets which we strung up along the pipes that ran beneath the ceiling. To Vernon the laboratory must have seemed like a circus tent. He walked in just as we were recording from three cells simultaneously. The three receptive fields overlapped, had exactly the same orientation, and were not quite in register, so that a line stimulus moving across them made them fire in turn. The implications for a possible columnar organization of visual cortex were very much on our minds, and cannot have been lost on Vernon.

Those cells, numbers 3007, 3008, and 3009, were actually numbers 7, 8, and 9, but we had decided to get

a running start by beginning at 3000, having seen a report by Vernon based on a series of over 600 cells. Vernon seemed suitably impressed by our series.

That first paper also showed that many cells receive input from both eyes, and that the two receptive fields, in the two eyes, were identical in their positions and orientations and general arrangement. We also could confirm David's finding of several years before, that some cells respond very well to movement in one direction but not at all to movement in the opposite direction. We found that for simple cells this directional selectivity could often be predicted from the relative strengths of the opponent subregions.

Our equipment was primitive. We did not even have a slide projector at first, but instead used a kind of magic lantern containing a light bulb, and we made our edges and slits by cutting them from cardboard. The animal faced a green blackboard onto which we pasted pieces of ordinary white typewriter paper, and on which we drew the receptive fields that we mapped. We put down a new piece of paper for every cell, and they all went into our protocol, together with the notes typed by Torsten on a venerable Underwood typewriter. Typing the notes was crucial, because we couldn't read each other's writing. This was of course long before the days of computers, so we were spared the time necessary to program them, and for that matter learning to program. Towards the end of the 60s we did obtain something called a PDP12, and David Freeman, our electronics engineer, joined the lab and was soon spending more and more time programming. But even then we were slow to use the computer except on cold days to supplement a bad heating system.

When I came in one morning, after we had given Steve our first abstract to look over, Torsten was looking very sad and said, "I don't think Steve liked our abstract very much". We reproduce it here complete with Steve's corrections (Figure 2), as an encouragement to young graduate students or postdocs when they first discover how hard it is to write, and to remind ourselves not to be too hard on our students when we find out that *they* can't write. The process of learning to write, consisting as it does of writing, submitting the product for criticism, rewriting, resubmitting, and endlessly re-revising, must have died out in schools, and not surprisingly, given how much it takes of a teacher's time. That first 1959 paper was read and criticized at least once by everyone in our group, and we completely redrafted it a total of 11 times. That was long before word processors—we did the typing ourselves. It was worth it. The *Journal of Physiology* wrote "Congratulations upon a very fine paper" and had no comments at all. The reviewer was probably William Rushton, but we shall never know for sure.

The Old Days

Steve was a wonderful mentor. He was fun and light-hearted. One week early in the winter of 1968 some lakes and rivers north of Baltimore froze over like mirrors. All of us (except for Steve—we were too sheepish to tell him) went one day and skated the entire day. When we came back Steve seemed slightly hurt, so for the

Single units were recorded extracellularly from (the) striate cortex of ~~the~~
lightly anesthetized cat. ^SW with the eye immobilized restricted light stimuli of
various shapes were shone on the light adapted retina, Most receptive fields
The Rec. fields of cortical
cells were analyzed and found to have an organization which
could be subdivided into excitatory and inhibitory regions, as found for
in many respects was similar to that of retinal ganglion cells (Kuffler, 1953). These regions mutually interacted,
so that a large spot covering the entire field was usually ineffective. However
excitatory and inhibitory areas were arranged in several types of specialized
balanced out others effects. ~~of this resulted in stimulation for a large~~
and complex patterns, and specific stimuli were required for effective driving. In many
cases being ineffective & pattern, ~~it was difficult to find the best stimulus~~
concentric receptive fields described for retinal ganglion cells were not seen
In the cortex. For example, frequently an excitatory ~~and~~ inhibitory region was
long and narrow with areas of opposite type to either side only. Such fields
were oriented in a vertical, horizontal or oblique manner. The two ~~flanking~~
regions were often but not always equally distributed, ^{Symmetric or} on the two sides of the
central area. They gave the strongest responses if a slit oriented
in the longitudinal axis of the field ^{or the stationary} was ^{flashed} ~~flashed~~ across
onto the retina with appropriate position and orientation gave (the strongest)
responses. If slits were stationary or moved transversely across
responses. Responses to transverse movements of slits were also dependent on
the slit orientation. Many units could be binocularly activated, and when
mapped out in the two eyes separately, the receptive fields were found to have
a similar organization.

Figure 2. Abstract for Federation Proceedings, Typed by Hubel and Wiesel in 1958 and Commented upon (or Torn Apart) by Stephen Kuffler

rest of that unforgettable week we all went, with wives and children. Steve was never harsh or openly critical when we expressed ideas or showed him something we had written, but made his feelings clear either by being

very enthusiastic and excited when he liked something, or vague and puzzled when he didn't. He took a keen interest in writing for its own sake: we all read and discussed and laughed over Strunk and White, Gowers'

Plain Words, and especially Fowler's *Modern English Usage*. Steve hated pompous writing: he said the word "yield" reminded him of sword fights, and to him "utilize" for "use", "visualize" for "see", and "individual" for "person" were abominations. He had a high threshold for understanding text, and kept insisting that one "spell things out". The object of writing was to make the ideas clear and flow easily, and to avoid tripping up the reader. He helpfully insisted that we measure and state our stimulus intensities, in log units. This we thought silly, because our cells seemed not to care about intensities or even about exact levels of contrast, but he said that without the measurements no one would take our work seriously. The purpose of figures, to his mind, was to convey and illustrate ideas, not to prove that one had done the work, but he was realistic about conforming to scientific fashions. We all drew our own figures, often using a horrible contraption called a Leroy, and Steve would refer to the process as "faking up a figure".

Many aspects of research were easier in those days. Grant requests were written in days, not months, and one seldom heard of a request not being funded. The National Institutes of Health, and in our case the NIH Eye Institute, had just entered a period of strong and generous research support, which together with a major influx of research talent from postwar Europe and a flexible and lively university system, with no competition from the ossified universities of continental Europe and Japan, marked the beginning of a huge burgeoning of biomedical research in the USA. As postdocs we had no theses to worry about—it is still far from clear to us that to be forced to write a book-length tome before one has ever written an abstract is good training. Who could ever correct a thesis manuscript in the detail that Steve corrected that first abstract, and what theses would ever be rewritten 11 times? To us writing was a major, time-consuming undertaking, and we avoided writing up the same work more than once by finding excuses to decline invitations to symposia that required written manuscripts. We never wrote reviews, not being scholarly by nature, and knowing that reviews soon go out of date.

In the spring of 1959 Steve was offered a professorship at Harvard and the entire laboratory and their families moved with him. The two of us had just been promised assistant professorships at Hopkins, but at Harvard we were demoted to a position they called "Associate", which came between instructor and assistant professor. This was slightly galling to us but Steve found it amusing, and assured us that promotions would come soon enough, either at Harvard or somewhere else. Harvard itself, at least the Medical School, seemed ponderous and stuffy compared to Hopkins Medical School; we missed the bustling hospital atmosphere and the daily contact with neurologists and ophthalmologists. But we had more space: to begin with an entire 400 square feet for our lab plus two desks. We soon added another 400 square feet for histology and hired a technician to do staining and sectioning, but we continued setting up our animals and tidying up after experiments, finding that it took one-tenth the time that it took a technician, and that it helped to be able to find instruments when we needed them. Our move to Boston was not traumatic,

at least after we got used to the terrible Boston traffic and drivers. Hopkins allowed us to move all our equipment (except for one precious Zeiss dissecting microscope with a floor stand), and as we were packing up Steve called from Boston to urge us to at least leave the windows.

Monkey Optic Nerve and Cat Geniculate

We had the feeling of being in a rich orchard, with lots of fruit ready to pluck. We recorded from the monkey optic nerve, because no one had yet looked at the behaviour of ganglion cells in a primate. We studied cells in the cat geniculate, just to make sure that the transformations we were imputing to the cortex had not already taken place at a lower level. The cat geniculate work brought an unexpected surprise, in that it proved possible to record from a cell body and simultaneously from one of its optic nerve afferents—usually the sole excitatory afferent—and show that the fields of the two were superimposed but that the geniculate field had a far stronger surround antagonism than the field of the retinal ganglion cell. This was very satisfying since it proved for the first time that the geniculate is not a mere relay station passively handing on to the cortex the information it gets from the eye. A few years later Cleland, Dubin, and Levick (Cleland et al., 1971) improved on the technique by the tour de force of recording simultaneously from a geniculate cell and the ganglion cell in the retina that formed its main input, and confirmed the hints we had seen that some geniculate cells are supplied by more than one excitatory afferent. A curious feature of this result is that nothing in the known anatomy of the geniculate could have predicted the main findings, that typically a cell was dominated by one or a very few cells, and that the field surround was enhanced. This apparent discrepancy between anatomy and physiology still has not been clarified.

Cat Cortex, Second Paper

By 1962 we were ready to write up what we still consider our favorite paper. For those days it was of blockbuster length, and could easily have been three separate papers, but it gave us much satisfaction to write something more ambitious and to show the dean that we weren't about to stoop to splitting our papers to increase the length of our bibliography. The paper described simple and complex cells, and showed how the simple cells could be imagined to come before the complex ones in an ascending hierarchy. It described the cell-to-cell variations in ocular dominance and set forth the 7-group classification that was to be so useful in the later deprivation studies. Finally it gave evidence for a columnar parcellation into two independent systems of columns, for orientation and ocular dominance. Of the two, the ocular dominance subdivisions were less striking and we were cautious in describing them; not until we studied cats with induced strabismus, and normal macaque monkeys, did we become totally convinced of their existence. Of course, the many types of anatomical demonstrations that were developed for demonstrating ocular dominance columns in the late 60s and the 70s ultimately made both their existence and their shape and

arrangement very clear. The most esthetically pleasing aspect about the paper was its strong suggestion that the orientation columns serve the function of gathering together the very cells that we were postulating must be connected in the circuits that we were proposing. Also, with its 1959 companion describing simple cells, it represents the first description of a clear function for the cerebral cortex, in terms of clear differences between input and output. It was followed by a short paper on the mapping of orientation columns in cat, showing that the columns extend from surface to white matter, and that viewed from the surface they can have a high degree of order, with progressive systematic shifts in orientation clockwise or counterclockwise. This was the first indication of the crystalline order that became much clearer in the late 60s and early 70s, particularly in the monkey.

Deprivation Studies in Cats

Meanwhile we had begun a completely different set of experiments, ones in which specific questions were asked, as opposed to exploration. It is not that we felt that the kind of science that explores, in the manner of Columbus sailing west, or Galileo looking at Jupiter's moons, or Darwin visiting the Galapagos (often pejoratively referred to as "fishing trips"), is in any way inferior to the science we learn about in high school, with its laws, measurements, hypotheses, and so on. Exploration had dominated our work up to then, since we had certainly had no "hypotheses" as we set about to explore the visual cortex. Neither were we in any way "quantitative" in our approach. The term "anecdotal", a favorite expression of disdain on NIH pink sheets, probably best describes the nature of most of our work, but the deprivation studies were slightly different in that we did ask somewhat more specific questions, without, to be sure, having anything that a modern study section would call a hypothesis.

The deprivation work was the clearest example of research that reflected our clinical backgrounds. We both knew about the blindness, described by Von Senn, that comes about as the result of congenital cataracts when their removal is delayed to childhood, and how refractory it is to recovery. We knew about the loss of stereopsis and the amblyopia that can accompany childhood strabismus, and about the blindness produced in animals brought up in darkness, as described in the work of Hebb, Riesen, and others. By 1963 we felt we had a good enough grasp of the behaviour of normal cortical cells to be able to recognize anything but very subtle changes brought about by deprivation. The irony is that had we set out in 1958 to tackle questions such as these, the sensible place to start would have been the retina, and we probably would have gotten nowhere.

We discussed the best procedure for raising kittens with no patterned visual experience, and rejected dark-rearing as too cumbersome. We settled for surgically closing the lids of one eye just before the time of normal eye opening (10–12 days after birth). When we surgically closed the eyelids of one eye in a litter of newborn kittens, we had no well-formulated hypothesis, or in any

case the two of us had no common hypothesis; it came to light years later that one of us thought we were closing the eyes to learn whether the connections responsible for orientation selectivity and so on were present in the newborn, whereas the other thought we were doing it to see whether the deprivation would interfere with the connections in the eye or brain. At the time, closing the eyes simply seemed an obviously interesting thing to do, and we probably never discussed our motives or indeed even formulated them explicitly to ourselves. It is curious to reflect, incidentally, that we never thought it necessary to write a grant request to cover any of the work that led to these six deprivation papers. That was lucky: it would have been a nuisance to try to formulate exactly what it was we were trying to learn, and there would have been a serious risk in widely advertising our plans. We wanted to finish the cat work and take our time writing it up, and then go on to repeat the study in the macaque monkey. It would have been annoying, to say the least, to see another group leapfrog over us and proceed to the monkey while we were writing up the cat results. Science is not the pure altruistic pursuit that many dreamers would like to believe.

The result of the first set of papers was that an eye-closed kitten becomes blind in the closed eye; that cells in the cortex lose their responsiveness to the eye that had been closed; that the unresponsiveness to a closed eye is far less marked if the other eye is also closed; that the retina and geniculate remain substantially normal, at least in their physiology; that cells in the corresponding geniculate layers become pale and shrunken, though they still respond to visual stimuli; and that the results are similar even if vision is occluded by a translucent occluder, rather than by eye closure. And finally, in newborn kittens that have never used their vision, one can find cells that have orientation selectivity and respond to both eyes in near-adult fashion. This last finding raised a storm of controversy, perhaps because in postnatal kittens many of the cells are sluggish and some do lack orientation selectivity. We felt that if *any* cells were orientation selective it proved that that characteristic does not necessarily arise through visual experience. The cat was perhaps not the ideal animal in which to ask this question, because it is so immature at birth. The eyes do not even open till around the tenth postnatal day. The macaque monkey, in contrast, is looking around taking a keen interest in his (or her!) surroundings the day after birth, and when we recorded from newborn monkeys right at birth we found cells whose physiology was hard or impossible to distinguish from cells in the adult. We felt that the controversies over these results were not purely scientific; in the 60s it was not politically correct (to borrow an expression from the 80s) to suggest that the newborn brain is anything but a tabula rasa on which the environment writes its messages. Previous work by psychologists on visual deprivation had generally been interpreted on the assumption that the blindness was caused by failure of connections to develop, rather than through impairment of connections that were present at birth.

It took us several years to answer some of the questions that were raised by this initial work. In defining the length of what became known as the "critical period",

each animal came to be represented by a point on a curve, and when we came to study the recovery obtained by reopening an eye that had been closed, all the work had to be repeated. And of course it all had to be repeated when we finally came to study newborn macaque monkeys. All these deprivation studies went in parallel with work in normal animals, and extended well into the 70s.

We were in for some major surprises. Sewing shut both eyes rather than just one, and finding that the cortical impairment was far less than would have been predicted from the single-eye closures, meant that the deterioration of connections could not be caused simply by disuse, but must involve competition between the two eyes for control over the cells. The same conclusion was indirectly supported by the results of cutting an eye muscle in newborn animals to produce an artificial strabismus. As already mentioned, these experiments, like the eye closures, were directly motivated by the effects of strabismus in humans—the blindness that often occurs in one of the eyes and, when visual acuity is unimpaired, the loss of stereopsis even after the muscle imbalance is surgically corrected.

Ironically, as a result of the deprivation studies we became identified in some people's minds with a philosophy that says the brain is "hard-wired", when one of the main things we thought we had shown was that in early life neuronal connections are only too subject to modification by the environment. What impressed us was the specificity of the changes that resulted from very specific insults such as squint and form deprivation, and the possible lessons for psychiatry, in cases such as early social deprivation or molestations. Perhaps Freud could have been right, after all, in concluding that much psychiatric illness results from events that occur early in a person's life. We were, of course, impressed by the degree of wiring already present in the newborn animal. To the degree to which we formulated any theories at all, we were probably wrong in supposing that the wiring, because present at birth, must necessarily be the direct consequence of genetic instructions: we underestimated the importance of prenatal neural activity on connections. Our attitudes have changed in these respects, to no small extent (if we may say so!) because of work by former graduate students and postdocs such as Carla Shatz, Michael Stryker, and Bill Harris.

The squint project had an amusing history. We began in the hopes of producing amblyopia by cutting an eye muscle and for no special reason chose to cut the internal rectus. We began with a litter of half a dozen kittens, and soon had 12 wall-eyed animals walking around the lab. But when we tested their vision, after a few months, by putting an opaque contact lens over one and then the other eye, it became clear that there was no impairment in either eye. We concluded the project was a failure and wondered what to do with all the kittens. We discussed whether we should bother to record from the cortex of at least one kitten, even though we could not imagine what we could possibly expect to learn. In the end it was easier to shoot a day and record from one animal than to go on discussing what to do.

At first the cells seemed perfectly normal, as we had expected. Slowly, however, we began to realize that

they were far from normal; almost none of them could be driven from both eyes, compared to 85% in normal cats. As we advanced the electrode, cell after cell was monopolized by one of the two eyes, then suddenly there was a complete shift to the other eye, which held the monopoly for a while and then gave way to the first eye. The grouping of the cells into separate eye domains was almost as surprising as the fact that they were all monocular, for until then we had only been vaguely aware of the division of cortex into left-eye and right-eye domains—the ocular dominance columns. In the normal cat this segregation is far less striking than in macaques, and it took these strabismus experiments to bring it out, by transforming cells that only slightly preferred one eye to cells monopolized by that eye.

So in the end we did find a good use for the wall-eyed kittens. We seemed to have achieved a dramatic change in neural connections simply by interfering with the normal temporal relationships between two sensory inputs, without interrupting either. The possible implications for learning, conditioning, and the Hebb synapse were clear, and exciting.

The deprivation studies provided us with fuel for research for two decades. In the 60s it was mainly confined to cats, whereas in the following 10 years we worked mainly with macaques, with essentially the same results, except that in monkeys we could take advantage of the cleaner subdivisions of the cortex into ocular dominance columns. Also we took advantage of a host of new anatomical techniques, starting with the Nauta method, then the axonal transport of radioactive labels and horseradish peroxidase, and finally deoxyglucose uptake. All these methods we used first for demonstrating the columns in normal animals, and then we applied them to deprivation.

By the mid-70s work in deprivation had developed world-wide into a small industry. Soon investigations were being made using many varieties of deprivation, for movement in specific directions, for specific orientations, and by disabling one or both optic nerves with substances such as TTX. Although the procedures were entirely painless for the cats and monkeys, the work seemed to have a great attraction for animal-rights people, who made much use of pictures of kittens with one eye sewn closed. Ironically, of all the research we did the deprivation work had the most important and direct clinical consequences. Our clear evidence that in cats and monkeys the period of plasticity—and hence the period in which recovery could occur—was limited to the first months encouraged ophthalmologists to begin operating on children for strabismus as early as possible in order to avoid amblyopia. It was good to be able to tell animal-rights advocates that our work had contributed in a major way to preventing one of the main causes of blindness.

In the decades that followed, the deprivation work had another indirect consequence. We discovered that our monocular closures in the monkey had striking anatomical effects on the eyeball of the closed eye, causing it to become longer and producing a florid myopia of 10 diopters or more. In the hands of Torsten and Elio Raviola this became the most important experimental model for studying what is probably the commonest

abnormality of the eye. It reinforced our parents' superstition that reading in poor light is bad for you, and suggested that people of oriental extraction are myopic not only for genetic reasons but perhaps also because of the microscopic characters they are forced to read.

Monkey Lateral Geniculate

One of the most satisfying studies in the 60s was the work we did in the monkey lateral geniculate body. In 1920 Minkowski had shown that each of the six geniculate layers is supplied by only one eye, but little had been learned about the layering since then. Speculations had been made, for example, that the three pairs of layers represent three primary colors. Except for the opponent color responses first seen in macaque geniculate by DeValois and colleagues in 1958, little had been added since Minkowski.

We were interested mainly in the relationship between the spatial-opponent effects Kuffler had described in the cat retina, and which we had found in the cat geniculate, and DeValois' opponent-color interactions. We surveyed the monkey geniculate at a single-cell level, mapping receptive fields, using white light and monochromatic light and looking at responses in dark adaptation. What resulted was a kind of taxonomy: a description of the main cell categories in the four dorsal layers, which we called types 1, 2, and 3, and the rather bizarre type-4 cells that are most characteristic of the ventral layers—bizarre in their profound and sustained inhibition by long-wavelength light but not by white light, implying some form of color-opponency, and their lack of any color selectivity in their phasic responses. One of the most surprising findings concerned the type-1 cell, which is by far the most common type in the four dorsal layers. Their receptive fields were opponent center-surround, with the center and surround dominated by different cone inputs—for example, red center versus green surround. This form of opponency was strange and surprising since it was just the opposite of what one would have expected as a basis for color contrast, or for what psychophysicists term "color constancy". We still have no clear understanding of the function of these cells. They form the overwhelmingly most important input to the cortical upper layers, which seem to show little interest in color, and partly for this reason we now suspect that it is the type-2 cells, rather than the type-1, that subserve our color vision, and that type-1 cells have their main role in form vision. Of course that leaves their color opponency unexplained.

Beyond Area 17

Since the beginning we had to restrain ourselves from plunging ahead into visual areas beyond the striate cortex. In 1950 Thompson, Woolsey, and Talbot at Hopkins had accomplished the almost incredible feat of mapping out Visual Areas 1 and 2 in the rabbit and monkey (Thompson et al., 1950). Their techniques were decades ahead of their time: they stimulated using tangent-screen projection; they localized their stimuli in the retina using what we now call the "reversing ophthalmoscope"; there being no microelectrodes for extracellular work, they had had to depend on evoked potentials, a

technique that is, ironically, more difficult than single-cell work; and in the cat, the striate cortex was not yet clearly mapped anatomically—its boundaries, especially as defined cytoarchitectonically, are far from crisp. Early in the 60s we wrote Talbot to ask him if he thought striate cortex corresponded to his Visual 1, or to both Visual 1 and Visual 2, and to our surprise he replied that he thought that the striate cortex was made up of the two areas. It was not till 1962 that Otsuka and Hassler (1962), in Jung's laboratory, finally succeeded in defining cat striate cortex using myelin staining, and established that Talbot's Visual 1 was certainly the same as striate cortex. It was only years later that it was shown that in the cat Visual 2 gets a strong direct projection from the lateral geniculate, quite unlike Visual 2 in the primate.

But in 1965 we at least knew where the cat 17–18 boundary was. The outer boundary that Visual 2 (or area 18) makes with what was then called area 19 was anyone's guess. Our recordings soon showed that Talbot and Marshall's topographic mapping had been correct: 17 and 18 were mirror images. The fields in 18 were larger and moved out rapidly as we recorded more and more laterally. Otherwise the recordings were disappointing at first, in showing nothing dramatically new. (We of course knew nothing about x and y cells—that was to come only in the 70s, during which we continued to ignore the distinction.) Suddenly, as we continued to go further and further laterally, into what we called "Visual 3" or area 19, the fields became smaller, began to march back towards the midline, and they became on average far more complex. These were the first "hypercomplex" cells, now termed "end-stopped". Their main characteristic was an optimal response to short line segments and little or no response to long lines. As often happened in that decade, the discovery of these cells came about almost by accident, and it was in the course of a single experiment that we came to realize that we had a new breed of cell. Thus we first found hypercomplex cells in cat area 19, but to be sure that they were peculiar to 19 we went back to 18 to look for them there—and found them. So when we wrote up the study, in another mammoth paper, hypercomplex cells appeared to us to represent a further level in the form-perception hierarchy, first appearing in 18 and reflecting a principle of increased elaboration of form perception as one went from one level to the next. Had we had the sense and will-power we would have gone back to 17 and checked there, and it was not till 1968 that we finally discovered hypercomplex cells in area 17 of macaque monkey. This motivated us to revisit cat cortex, where we did indeed find them, though they were less common than in macaques. Given the choice of working year after year at the same problem or going on to new places and trying new things, our personalities seemed to fit the second of these approaches, despite the risks.

Terminologically also the hypercomplex cell had a spotty history. In 1968 Geoffrey Henry, whom we met at a meeting in Australia, told us that Bogdan Dreher in his laboratory had seen cells in area 17 of cats that preferred short lines but that otherwise seemed to be more like simple cells (Dreher, 1972). This was a blow to us, as it suggested that his cells might be formed directly from geniculate afferents, as a variant of simple

cells, and that our hypercomplex cells might be formed from his simpler ones. The hierarchy was more complex than we had realized. Before too long Charles Gilbert, a graduate student in our laboratory, confirmed the presence of end-stopped simple cells in cat striate cortex, and we began to drop the term "hypercomplex" in favor of "end-stopped" (Gilbert, 1977). Ironically, perhaps, we have never seen such simple-hypercomplex cells in macaque monkeys, so that the argument for dropping the term "hypercomplex" in primates seems in retrospect rather weak. On the other hand the word never seemed esthetically appealing, and "end-stopped" is more descriptive.

Our final foray into areas beyond striate cortex was at the very end of the decade, when we recorded in the cat from a region lateral to area 19, that had been discovered by Margaret Clare and George Bishop (Clare and Bishop, 1954). We found a crude topography, with vigorous responses to moving lines and enormous receptive fields but, to our disappointment, the cells seemed even less elaborate than the ones we had seen in area 19, in terms of form analysis. This area later came to be called "PMLS" and is clearly the homologue in the cat of what in primates is now called MT, or Visual Area 5. We also recorded a few hundred cells from macaque MT, in the late 60s, before it had been named or defined anatomically, but we found the cells boring, as we had found those in the Clare-Bishop area, and we decided not to write the work up. So we missed out on what is now considered one of the more interesting areas in the monkey occipital lobe, an area whose main preoccupation is the analysis of movement. This was the dawn of a realization that what had previously been called area 19 in the primate actually consists of very many topographic representations of the visual field, perhaps as many as two dozen. It was also just before the realization that beyond areas 17 and 18 the visual path splits into multiple components, with different areas specialized for one or another visual submodality, such as color, form, movement, and stereopsis. The visual system, then, was organized in many parallel subpathways, each with its own hierarchical organization. The demonstration of the x- and y-type retinal ganglion cells in the Enroth-Cugell laboratory (Enroth-Cugell and Robson, 1966) was perhaps the first evidence for this parallel processing, subsequently followed up at higher levels in the 70s and 80s by Jonathan Stone, Semir Zeki, David VanEssen, Jon Kaas, John Allman, and others.

Macaque Monkey Striate Cortex

On first recording from monkey striate cortex, some time in the early 60s, what surprised us most were not the differences between monkey and cat, but the similarities. We saw all the receptive field varieties that we had found in the cat (simple, complex, etc.), and only when we looked more closely did any species differences appear. With smaller fields and more precisely defined orientation selectivity, we had the impression of dealing with a Rolls Royce rather than a Volkswagen. We were certainly pleased at this result, since it suggested that our work probably applied also to humans, given that we are far closer to monkeys than monkeys are to cats.

The biggest differences between monkey and cat were in layer IV, which in cat seems to contain no center-surround cells, in contrast to the monkey, where such cells form the overwhelming majority. It was as if in macaques orientation selectivity had been postponed for one stage. The biggest surprise was the relative scarcity of color-selective cells, which we had expected to see in abundance given their abundance in the four dorsal geniculate layers. We found orientation-selective upper-layer cells that responded to red lines but not to white lines, but we almost never saw cells with comparable preferences for green or blue lines, and those that preferred red lines comprised no more than 10% of upper-layer cells. The blobs, with their color-opponent cells, were not studied physiologically till the end of the 70s, probably because it was only then that they were revealed anatomically through Margaret Wong-Riley's use of the stain for cytochrome oxidase. It is clear from our old protocols that we had recorded from cells in blobs, but we failed to note their color selectivity or their center-surround organization, and ascribed their lack of orientation selectivity to injury by the recording electrode or some other pathology.

We recorded from monkey cortex for several years before we became aware of the striking orderliness in the arrangement of the orientation columns. In one memorable experiment, in a penetration that happened to be oblique to the cortical surface, we began to notice that each successive orientation was shifted by a small angle, about 10 degrees, from the previous one. As the electrode advanced the progression was consistently clockwise for about 20 shifts, all within 1 millimeter, and then the progression reversed; this again lasted for about a millimeter, and then another reversal took place—and so on. After 5 hours, in which we did not leave our chairs, we had recorded 54 shifts in orientation. We had never before seen such order, though we had seen hints of it in our mapping of cat cortex in the early 60s. We later found that by making very oblique penetrations, observing multi-unit background activity continuously as we advanced the electrode, and by plotting our orientations against electrode-track distance, we could see this orderliness in nearly every penetration, and we became convinced that it is a constant feature of the striate cortex. What we still lacked was an anatomical means of producing a two-dimensional map of these orientation domains, and for years the sudden breaks in continuity that we occasionally saw, and the reversals, remained a mystery. It was only in the 80s that the orientation maps were finally revealed through the development of optical surface-mapping techniques by Gary Blasdel and Amiram Grinvald.

Anatomical Demonstration of Ocular Dominance Columns

One of the last papers of this decade reflects a major new trend that began in the early 60s and continued through the 70s. This was the revolution in neuroanatomical path tracing, set off and for years dominated by the silver fiber-degeneration staining technique invented in the late 50s by Walle Nauta. Previous methods such as Wallerian degeneration, retrograde degeneration, and the Glee's technique, were limited and crude

by comparison: suddenly it became possible to make a lesion in one part of the brain and find its projections with high reliability by stains specific for degenerating fibers and especially degenerating terminals. The method was rather tricky and it was assumed that it was for professional anatomists only. One day James Sprague, an acknowledged expert in the Nauta technique, phoned us to ask if we might be interested in hiring his chief technician, Jane Chen, who for personal reasons had to move to Boston. We had used anatomy as a tool for years to find our micro-lesions and to reconstruct our electrode tracks, and though it seemed preposterous to branch out into this forbidding method in experimental anatomy, we decided we had little to lose.

It occurred to us that in the microelectrode we had a tool that we could combine with anatomical path-tracing with powerful effects. To identify our recording sites we had been making electrolytic lesions a few hundred micrometers in diameter for years. Because making lesions had no adverse effects on the electrode, one could make many in a single track. So we hit on the idea of making lesions after identifying a site by recording, allowing the animal to recover, and staining the tissue with the Nauta method a week later. The first major application was to make lesions in a single layer of the monkey lateral geniculate body. This allowed us to establish that the sites of termination were layers 4A and 4C, and not 4B (the line of Gennari) as had previously been thought, and that the magnocellular layers terminated at a level in 4C that was clearly above the terminations of the parvocellular layers. These magno and parvo sublayers were later termed 4C-alpha and 4C-beta, by Jennifer Lund. Our main purpose in this experiment was to reveal the ocular dominance columns, and this succeeded beyond anything we had dared hope. It allowed us to actually see them, and showed at last that they were parallel stripes.

In the 70's we went on to do similar mapping with radioactive tracers that we micro-injected into the geniculate or the vitreous of the eye itself, following Bernice Grafstein's demonstration that tracer injected into an eye of a mouse could be transported all the way to the cortex. These anatomical techniques added another dimension to the deprivation work, as we could now demonstrate morphologically the effects of eye closure on ocular dominance columns, and examine directly their postnatal development.

A New Department

In 1958 our original group came to Harvard as a part of the department of pharmacology. Physiology would perhaps have been a more logical place to house us, but pharmacology had just acquired new space, and Otto Kraye, its chairman and an old friend of Steve's, had pressed for his appointment as full professor, the first example at the Harvard Medical School of such a professorship held by anyone but a chairman. We were welcome and happy in pharmacology and Steve especially liked the freedom from administrative burdens. We never had formal group meetings, decisions mostly being made when several of us chanced to pass in the hall. Our group, in the early to mid-60s, was responsible

for 6 weeks of concentrated teaching to the first year medical class, which we shared with the neuroanatomists and with Elwood Henneman in physiology. We thoroughly enjoyed this teaching and took it very seriously, all of us attending everyone else's lectures, giving conferences, and attending labs (four students to a cat, in those days), and we dropped any attempt to do research. The course was one of the most successful ever mounted at the medical school, and it helped in broadening our knowledge by forcing everyone to teach everything. It was too good to last, and ultimately died because of the compulsion of medical school faculties to change the curriculum at least every 5 years. We went back to teaching separately from the neuroanatomists, usually teaching the physiology *before* the neuroanatomy course.

We had meanwhile become what was probably the leading group of neuroscientists anywhere, in a field that was rapidly evolving so as to include physiology, anatomy, and chemistry. This had the effect of overcoming the limitations imposed by having the three subdivisions each housed in a separate department, with no intercommunication. All over the world the distinctions were becoming blurred, and have continued to fade in subsequent decades.

By the late 60s our group had become too big to reside reasonably in the pharmacology department with its very different aims and interests—the tail had come to wag the dog—and a break was clearly in order when the time came for Otto Kraye to retire as chairman of pharmacology. Though it did not seem likely that Harvard would take such an earth-shaking step as to form a new department, it seemed the only reasonable solution. Luckily our Dean, Robert Ebert, was open to new ideas, and the Dean at Harvard Medical School had the necessary power: any faculty resistance was overridden, and we suddenly had to think up a new name for ourselves. The result was "Neurobiology", and as far as we know this was the first official use of the term. The transition to a new department was not without some problems: for a time it seemed that the department would be split when David was offered, and for a brief time accepted, the chairmanship in physiology. The arrangement failed despite the friendliness and cooperation of the physiologists, largely because the notion of a single department devoted to the nervous system was too powerful. Also our research was going too well to risk weakening it by a substantial commitment to administration. For Steve, to become a department chairman was less of a handicap because our group was so close-knit: we still never had faculty meetings and decisions seemed to be made by common consent. Things changed in the 70s, sadly, because Steve and the two of us could not go along with a trend in which more and more time had to be spent on social issues, and some of the camaraderie and cooperative spirit were dampened. We all paid a price for the illness that seemed to creep over the country in those years.

Summing up

As we look back over the period of the 60s and 70s what stands out most in our minds is the fun we had.

We came into a new field and seemed to have carte blanche to do whatever we liked. What in retrospect mainly characterized our styles was a technical simplicity, amounting almost to sloppiness, and a relative freedom from theoretical constraints. We hesitated to invest heavily in a technique until it became very clear that we really needed it. In the case of the Nauta method and the acquisition of a histological technician, the investment paid off. An investment in an electron microscope near the end of the 60s failed when we lost interest in obtaining sharp pictures, and the instrument gathered dust. We were very late to adopt the use of computers: our research may have suffered as a consequence. It is impossible to assess the trade-off between whatever we missed and the time it would have taken to learn to do the programming. Meanwhile we were also spared the drawing of graphs and statistical evaluations for which computers are so useful.

In 1960, theories as to how the central nervous system might work seemed to us to be contributing little to understanding the brain; we inserted our electrodes with no major preconceived ideas as to what to expect. We did have a vague faith that it was the connections that counted, and the assurance, mainly from the work of Ramon y Cajal, that the connections were orderly and beautiful, with little element of randomness. As the decade progressed, new theoretical constructs—that the brain was a Fourier analyzer, that linear systems analysis had something to offer, that Gabor functions or Gaussians were worth knowing about—seemed wild to us, to the extent that we could understand the ideas at all. At times we have felt alone in this conservatism, but we are encouraged when we reflect on how free such fields as evolution and molecular biology have been from such heavily computational approaches. This is not to deny the importance of theory to fields such as physics or even some aspects of biology, but only to suggest that each field has its own style, and that either theory has a different and lesser part to play in neurobiology, or that neurobiology is not quite ready for a mathematical approach.

Today we are struck by several huge differences between now and the 60s. The field has expanded out of all recognition; we go to meetings of the Society for Neuroscience, now with registrations of 25,000, compared to a few hundred in the 60s; during the meeting, every day there are one or two sessions on V1 alone and one or two on visual deprivation. While the field has grown, so has its financial support, but not in proportion, so we have the strong feeling that we were active at the right time, with enough money for our research and far less anxiety. We don't envy the competition young neurobiologists face, or the time they have to squander writing grant applications.

Directions of brain research have changed, not surprisingly. Two powerful trends have taken off in opposite directions. First, and most prominent in terms of resources, is the push toward the cellular and molecular levels. One has the feeling that this movement is represented by 23,000 of the 25,000 who attend our annual meetings. No one could possibly deny the importance of the knowledge that is coming out of this emphasis. At the other extreme, and just as important, much of

the work done today in the central visual system is in awake, behaving animals, especially monkeys. As a consequence, in vision inroads are rapidly being made into the two dozen or so visual areas that used to be called "area 19", to say nothing of vision-related areas in temporal, parietal, and frontal lobes. Each area can be investigated without the disruption that anesthesia causes to the firing of cells, and to behavior. It now is accepted that beyond the primary visual area and V2, the pathway diverges into subdivisions in which quite different aspects of vision are handled—form, movement, color, stereopsis, and so on. This does not mean the absence of any hierarchical organization; on the contrary it implies many hierarchies working in parallel. Best of all, perhaps, the style of working in awake, behaving animals involves recording not in stints of 24–36 hours, or till one collapses from exhaustion, but for just a few hours a day, or until the monkey gets fed up with fruit juice.

Meanwhile we confess to a nostalgia for the approach we took during those 25 years from 1958 on, in which we worked at a level that asked about the detailed functional organization of cortex: the repertoires of cells of different classes, the layers and the columns. We feel nostalgia not just for old times' sake, but because the work is so fascinating and there is so much still to do. Area 17 is off to a good start (we hope); 18 (V2) with its thick, thin, and pale stripes, is known in about the same sketchy detail as 17 was in 1970; in MT we know a lot about function, thanks to Zeki, Movshon, Newsome, Born, and others, and we know of several column types. But for most of the other few dozen areas we have little of this kind of knowledge. Awake-behaving techniques, powerful as they are, haven't so far lent themselves to the coupling of physiology and anatomy that is required for getting at functional organization, and so functional organization is languishing. We hope that in the future technical advances will make it possible to combine the two approaches.

Fields of research are subject to fashions. At present, the detailed (some would say, plodding!) area-by-area analysis is being eclipsed by the excitement and vigor of work at the molecular and awake-behaving levels. That is as it should be, because research has to be done by people who are excited by what they are doing and find it fun. Meanwhile the problems in detailed organization will still be waiting to be taken up again when the interest revives.

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