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Montréal General Hospital (1951)
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American Academy of Arts and Sciences (1965)
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David Hubel carried out fundamental studies of the physiology and anatomy of mammalian visual cortex. Together with Torsten Wiesel, he identified the ocular dominance columns, the simple and complex cells of visual cortex, and demonstrated plasticity in the visual cortex following monocular deprivation.

David H. Hubel

I was born in Windsor, Ontario, in 1926. Both my parents were American citizens, born and raised across the river in Detroit. They had moved to Canada a few years before I was born, when my father got a job as chemical engineer for Windsor Salt Company. From the start my citizenship was complicated because the citizenship laws in Canada and the United States are different; I was considered Canadian by Canada because I was born there, and American by the United States because my parents registered me at birth as a U.S. citizen. Consequently, I had dual citizenship most of my life. All this had practical consequences: when in college, in the late stages of World War II, I had to serve in an Officers Training Corps in Canada, and in 1954 I had to serve in the U.S. Army because of the doctors' draft. In 1982 the Royal Society discussed making me a member but, by their rules, American citizenship precluded my becoming a regular member, and because of my Canadian citizenship I couldn't be a foreign member. Finally, after much correspondence and committee meetings on their part it was decided that for practical purposes I was an American. This meant I could append to my signature "For. Mem. R. S." instead of simply "FRS".

In 1929 my parents, my older sister and I moved to Montréal when Canadian Industries, Ltd., took over Windsor Salt. We settled in Outremont, in a middle-income neighborhood that was then about two-thirds French speaking and one-third English. "English", in Outremont, meant four-fifths Jewish, one-fifth Protestant (mainly Scotch origin). In our duplex the French landlord's family lived downstairs and their little boy and I played together constantly for about five years. The first French word I learned, at the sandbox behind the house, was "sable" (pronounced "sawb," meaning sand). We boys developed a half-French Canadian half-English polyglot which no one else could understand—I can still see our mothers shaking their heads and laughing as we jabbered away. In our lingo, "Pokapab" meant "I can't" (a corruption of "Je ne suis pas capable"), and "petayt" meant "perhaps". I have wonderful memories of our French neighbors, and Quebec still seems a great example of two cultures living in harmony and friendship, blighted mainly by trouble-making politicians plus a certain unwillingness of the English to work at another language. In promoting French-English relationships our Outremont Protestant schools were, if anything, a hindrance. We started French in grade three

and slugged away at French grammar, but absolutely no effort was made to teach us to speak or comprehend spoken French Canadian. The Quebec laws said that Roman Catholic teachers could not teach in Protestant schools, and so our French teachers were mainly Huguenots from France.

To a French Canadian our accents were ridiculous, and we could not buy a streetcar ticket using French without being laughed at. Some of the French did sink in however, and now I read French with pleasure. I can do reasonably well in a conversation, probably because the patients at the hospital where I interned were mainly French speaking. I, as the doctor, being as it were in the driver's seat, refused to talk to them in English and managed at last to get some practice in French. In the past few years I have even lectured in French, in Paris and in Montréal. The first time when asked over the phone for a lecture title by my University of Montréal host, I proposed "Oeil, Cerveille, et Vision". After a slight pause he politely said "Perhaps cerveau?" I asked what the difference was and he answered "Cerveille, c'est quelque chose à manger". I think the audience followed everything in the lecture (they laughed at the jokes, which I put in as controls), but they also laughed when for blood vessels I used "vaisseau saignant"—which means "bloody vessel".

Except for the deficient French teaching, our schools in Outremont were excellent. Most of the students were first-generation Jewish-European, and there was a seriousness of purpose that complemented the absence of television at home or computers at school. After school, during the winter, it was light enough to ski on the mountain for about an hour. Otherwise we went home and studied.

I got interested in science very early. I plagued my father with questions about chemistry, and a wonderful Lott's chemistry set (British made) slowly developed into a small basement laboratory. There I perfected an explosive based on potassium chlorate, sugar and potassium ferricyanide, that could be heard over all Outremont, rocked the neighborhood houses and brought two burly French policemen to our door. I told them I had simply put firecrackers in a toy brass cannon, and it must have all seemed innocent to them.

My other passion was electronics. Over what must have been an unselective crystal set I picked up the transmissions of a neighboring radio amateur, whom I got to know. I built a small one-tube radio that worked immediately, but then spent months trying to get a more ambitious short-wave radio to work. It produced a roar like a motorboat which I never succeeded in curing. Years later I finally learned that the trouble was feedback through the power supply, which could have been remedied in minutes with a capacitor and resistor in parallel. Not having anyone nearby to help, and no book besides a 1937 American Radio Relay Handbook which was about as easy to read as swimming through molasses (the 1993 edition is just as bad) and with no good libraries in Montréal, my electronics had to wait

until I got to college. Four years ago I finally did become a licensed ham, with a call AA1FG, of which I am inordinately proud.

Like most families in those days we had a piano at home, and both of my parents played a little and my sister took lessons. I learned from them, and started formal lessons at the age of five, before I could even read. I kept the lessons up through high school and much of college, and still play about an hour each day. My main teacher was one of the best organists in Montréal, and to him I owe a love of Bach that I would not trade for any amount of success in science.

In high school, 10 subjects were compulsory. In addition one had the option of choosing among biology, advanced mathematics and Latin. Mathematics was considered appropriate for future engineers, Latin for future doctors, and biology for dumb students. I chose Latin, not wanting to preclude medicine and having no interest in engineering, but I found the math so easy that I learned it by myself. Latin was not at all easy; I loved it and worked hard at it, harder than at any other subject except history. That was taught by the best teacher in the school, a tiny red-haired Irish woman named Miss Bradshaw, who made the students work like slaves and assigned an essay each week which she then covered with red ink, demanding that we produce ideas as well as facts.

I wanted to go to college in the United States, and went to Boston for an interview at the Massachusetts Institute of Technology (MIT) (my interviewer was a young enthusiastic man named F.O. Schmitt, whom I got to know well many years later). Because of World War II it became impossible to send money out of Canada, so I stayed in Montréal and went to McGill University. I commuted, which was not much fun, since taking the streetcar swallowed up 90 minutes a day. I decided to take Honors in mathematics and physics because these subjects fascinated me and there was almost nothing to memorize. That left time to attend every concert in the city and keep up the piano. Mathematics at McGill was excellent, physics was bad. Modern physics (relativity and quantum physics) was not taught at all to undergraduates. Instead we learned classical physics, including such utterly stultifying subjects as statics. Luckily it was classical physics, especially optics and electronics, that I ended up needing in my work.

After four years of undergraduate college I had to confront my first big decision. I had applied to graduate school in physics and had been accepted. More or less on a whim—and never having taken a course in biology even in high school—I also applied to medical school at McGill. Almost to my dismay I was accepted. Registration day arrived and I still hadn't made up my mind. When I finally decided on medicine I went to tell the professor who was to have been my advisor in physics. I can still hear him saying, "Well, I admire your courage. I wish I could say the same for your judgment!"

In the back of my mind, I suppose, was the idea that I might be able to apply my physics to medical research, and that if there were no opportunities in research, practicing medicine might be fun. I had been seriously intimidated when I attended an international meeting in physics in Montréal, while I was still an undergraduate: it was clear that my physics training had not got me off to a flying start, and I was shaken to see how crowded a field it was.

Medical school, on the other hand, was like a blow to the jaw. It took the first year, and four Cs at midterm to teach me that medical school requires work. Biochemistry was the only subject I really enjoyed and I did very well in it. Near the end of the first year, with all the class hopelessly behind, a kind anatomy professor told us that if we were really up against it we should remember that head and neck made up about half the work but could be the topic of only one of the five exam questions. The obvious solution was to skip head and neck. Ironically, I took his advice.

Near the middle of that first year I began to wonder if I had made a mistake; I had not made any effort to talk to people in research, to find out what the opportunities were. One day I went to one of the few professors at McGill who was actually doing research, a man who had, like myself, majored in math and physics. His comments shook me. He said, as part of a long soliloquy, that I should realize that the opportunities to do medical research in Canada were statistically almost nil, amounting perhaps to one job a year. But, he added, if I were to get that one job, the statistics wouldn't matter. One simply had to clench one's teeth and take a chance.

By second year medical school I began to develop a strong interest in the brain. Luckily for me the Montréal Neurological Institute (MNI) was part of McGill. It was one of the most celebrated neurological institutes in the world, best known for work on epilepsy by Wilder Penfield and Herbert Jasper. The MNI was perched high on the hill to the southeast of Mount Royal, a sort of ivory tower that medical students seldom climbed. I decided to grab the bull by the horns and made an appointment to see Penfield himself. Finally the day arrived. I borrowed the family car, parked it on University Street, and in a state of some terror climbed up to the fourth floor of the institute. Penfield was at his most charming, and when I told him of my physics background he immediately took me up to see Herbert Jasper, who in turn, immediately offered me a summer job doing electronics in his physiology group. (When I got back to the car I found it running, with the keys locked inside. I took the streetcar home to get a spare key, and 90 minutes later was back. It was a stressful afternoon.)

To my surprise, I enjoyed clinical medicine and even led the class in, of all subjects, obstetrics, which I liked even if it was free of intellectual content. By the end of medical school I had become interested enough in clinical medicine not to want to give it up, at least not so soon, so I decided to do a residency in neurology and in preparation did a rotating internship

(medicine, outpatient surgery, gynecology and mental-hospital psychiatry) at the old Montréal General Hospital, which was then in a slum, with mostly French patients and a wonderful atmosphere. I probably enjoyed that year more than any other, before or since.

The two summers I spent doing electronics for Jasper at the MNI were the start of a long association. After graduation and my internship, I did a year's neurology residency, followed by a year with Jasper doing clinical electroencephalography (EEG). Completely empirical, EEG was of great use in those days, long before neurology had become revolutionized by modern computer-aided imaging methods. Then, to diagnose brain disease, one did the usual history-plus-physical, an EEG, and finally, a hideous procedure called a "pneumogram", in which one drained off the poor patient's spinal fluid (about a tumbler full) and replaced it by air, causing a violent headache: x-ray might then show up such things as tumors, provided they were the size of a tennis ball. Of course, EEG found its main use in epilepsy, and Jasper was the undoubted world expert in that field, besides being one of the leading clinical neurophysiologists of his time. His scientific outlook was wonderfully broad and he had a clarity of mind and skepticism that made him stand out among brain scientists. The first time we spoke, the day of the locked car, he asked me what I had read in the field. I told him I had just read *Cybernetics*, by Norbert Wiener. He gave me an odd look, and said, "Did you understand it?" I thought I had, even if through a glass, darkly, and when I said so, he grinned. It was clear that he thought that Wiener's brain science was off the wall, but he was nice enough not to want to put me down.

I began learning EEG from Cosimo Ajmone-Marsan, who was then a teaching fellow at the MNI, and Jasper's main assistant. Ajmone-Marsan was a wonderful teacher, bright and witty, and I felt privileged to work with him. It didn't last: after three months he accepted a position at the National Institutes of Health (NIH) in Bethesda, Maryland, in clinical neurophysiology. The Clinical Center at NIH was just getting into full swing, and that year several of the best people at the MNI took jobs there. Suddenly I found myself Jasper's main assistant, having to read most of the EEGs of the institute and attending all the Penfield temporal lobe excisions. It was a busy year, which was to have been half research, but the research fell by the wayside.

All the fellows at the institute took part in a seminar series that covered neurophysiology. By some lucky chance Jasper assigned me the visual system, and by an equally lucky chance I came upon the 1952 volume of the Cold Spring Harbor Symposia, which was devoted to neurophysiology, and there discovered two great papers by Keffer Hartline and by Stephen Kuffler. These came like a sudden ray of light, as they seemed to be getting at the question of what the nervous system was doing to encode sensory information. I had no idea then that I would ultimately get to

know Hartline fairly well, and that Kuffler would become one of my closest friends and my main mentor.

One day, a young neurologist named Charles Luttrell showed up from Johns Hopkins, in Baltimore, to learn EEG, and Jasper assigned him to me. Luttrell must have found me a good teacher, because on returning to Hopkins he arranged for me to be offered the residency in neurology there. The time was certainly ripe for me to get out of Montréal and see something else, even though it meant again postponing starting research (I was 28, and still had not done any research even during summers—if you don't include my work on explosives in the 1930s). I was sure that with my dual citizenship I would be subject to the doctors' draft as soon as I set foot in the United States, but that didn't seem to be a valid reason not to accept (this was between the Korean and Vietnam Wars, but M.D.s were still subject to two years of military service).

I was married in 1954, the summer before the EEG fellowship. My wife, Ruth, had just graduated from Hebb's psychology department at McGill. We kept body and soul together by her taking a job as a technician in clinical psychology. Even for that time my income from the MNI, \$1,800 a year, seemed meager and prospects then, in research in Canada, were far from brilliant. In Baltimore our finances were even grimmer—my pay as a neurology resident was \$35 per month, of which \$18 was wangled through the kindness of Jack Magladery, then chief of neurology at Hopkins. Clinically, the high points of that year were the informal teaching of Frank Ford, the country's leading pediatric neurologist and a brilliant, thoroughly eccentric clinician, and the weekly Saturday morning clinics run by Frank Walsh, the world's leading neuro-ophthalmologist.

In 1954 Johns Hopkins was an exciting place. Everyone in the area, house staff, attending staff, people in research at the hospital and medical school, had lunch at the Doctor's Dining Room. At these informal meals, surrounded by dark paneled walls, people in neurologically related fields tended to sit together, and it was there that I first met Stephen Kuffler, whose lab was in the basement of the Wilmer Ophthalmology Institute. Despite his friendliness, it never occurred to me to visit his lab: I was much too shy and felt I had nothing much to offer. He was at that time working on synaptic transmission but kept up a vision project that was run by postdoctoral fellows.

My first meeting with the other Hopkins celebrity in neurophysiology, Vernon Mountcastle, occurred when a neurosurgery resident asked him over to the hospital to give an informal research seminar to the house staff. Vernon was, I think, dismayed by the neurophysiological naïveté of the neurosurgeons; I was the only one there who asked questions, which must have impressed him, as he still remembers that occasion.

The doctors' draft loomed and it seemed certain I would be grabbed after my neurology residency year was up. I made several trips to

Bethesda, hoping to get assigned to NIH. Luckily, I also visited the Walter Reed Army Institute of Research, where I first met Michelangelo Fuortes and Robert Galambos, who assured me that I would be assigned there if I volunteered for the Army. I did so, and after a close call in which I nearly found myself in Japan, I arrived at Walter Reed, an Army captain, finally about to begin doing research, at age 30.

In retrospect, I doubt that I could have found a better place to begin research on the central nervous system. Neuropsychiatry at Walter Reed consisted of a small group led by David Rioch, an authority on the thalamus and a well-known psychiatrist with a background in neuroanatomy. The group he had assembled included Robert Galambos, one of the foremost people in auditory neurophysiology and a close collaborator of the neuroanatomist, Jerzy Rose, who was then at Hopkins; Mike Fuortes, then working with Karl Frank at NIH; and Walle Nauta, recently arrived from Holland, the main forerunner of the dawning revolution in neuroanatomy. It was a small, close-knit and exciting group.

My first day at Walter Reed was unforgettable. I arrived in the morning and was greeted by Mike Fuortes, who was to be my advisor while I got started. Mike was preparing to set up a decerebrate cat for a spinal cord experiment. He began by asking if I had any experience anesthetizing cats. The answer was no. Had I ever set up a cat for recording? No. Had I done any experiments in neurophysiology? To every question, the answer was no. Mike walked calmly over to the window and gazed out for a few minutes. He then said, "Well, here is what I suggest. We'll postpone the cat to this afternoon, and this morning we'll set up a frog sciatic nerve preparation". So that was my crash laboratory course in neurophysiology—peripheral nerve physiology in the morning, and in the afternoon mammalian decerebration followed by one of the most difficult neurophysiological procedures: unroofing the spinal cord, dissecting the nerves to leg flexors and extensors and teasing apart a dorsal root to record from single isolated root fibers. It was a big day.

Mike had to go away for a day a few weeks later and it fell to me to run an experiment by myself. To be exact: by myself with massive help from a wizard technician named Calvin Henson, a wonderful, generous, witty man, and a friend of Duke Ellington, who could do anything surgical that anyone else could do, only better. Calvin and I were to work together for three years, and it is to him and Mike that I owe my research training in neurophysiology. "Doc, ya holler before you're hurt", Calvin would say when I would groan in anticipation of some terrible catastrophe like drilling into a cat's cortex.

Mike and I collaborated for about three months, and the work resulted in a modest single-unit study in the *Journal of Physiology* that compared flexor and extensor reflexes in decerebrate cats. Mike had a rare sixth sense for biology, and a breadth of outlook and tolerance of others' ideas that

made him a delight to work with. Before our paper was mailed off he commented, almost as an aside, that I should realize that the order of names on a paper in the *Journal of Physiology* was determined strictly alphabetically. I felt enormously flattered at this generous and slightly backhanded compliment, for it had never entered my mind that I should be first author.

Later that first year, the time came for me to get started on a project of my own. I had no specific ideas, though my years at the MNI had given me an interest in cerebral cortex and sleep. At that time, the world of neurophysiology was much smaller, and brain physiology was heavily preoccupied by studies of consciousness, sleep, the reticular system and something mysterious called "recruiting". Single-cell recording from cortex had only barely begun in the labs of Herbert Jasper and Cho-Luh Li in Montréal, Richard Jung in Freiburg and Vernon Mountcastle in Baltimore, and we hoped that these new methods would soon help us understand consciousness. Alas, studies of consciousness languished, perhaps for want of adequate methods or ideas.

Mike Fuortes made several suggestions as to possible projects. One seemed rather outrageous, but certainly adventurous. This was to expose the cortex of a cat and, using fine forceps, insert small wires (as E.D. Adrian had in the spinal cord) and then sew the animal up, hoping to record single cells after it had recovered and was wide awake and moving about freely. We made one or two attempts, but they were complete failures.

I decided that this project was well worth taking on but would require some serious tooling up. My first efforts went into making a microelectrode that would reliably record cells extracellularly without breaking or bending into hooks. Harry Grundfest had published a paper describing a stainless-steel electrode electrolytically pointed by raising and lowering it into a polishing bath and insulated with a coating called Formvar. I decided that stainless steel was not stiff enough, but I had no idea what other metals to try. By a great stroke of luck, the head of the instrument shop at Walter Reed was a physicist named Leon Levin, who had done his thesis in electrochemistry. He suggested I try tungsten, gave me a roll of it and said I should sharpen it with alternating current in a bath of concentrated sodium nitrite. The results were spectacular; within days I was able to make a pointed wire that looked ideal and was strong enough to pierce, with a little care, my thumbnail. It only remained to find a way of insulating the wire down close to the tip. That was not easy. I tried every coating I could find but nothing seemed adherent enough or viscous enough. Formvar did not adhere and in any case was available only in tank-car amounts. A solution of Lucite in chloroform came close to working. One day while I was playing with this my neighbor in the next lab walked in with a can of something called "Insulex" and said, "Why not try this?" I soon found that when Insulex was thickened by evaporation it became viscous enough to adhere to the wire, and suddenly I had an electrode that was recording sensational single units. I spent the

next few months recording everything in the anesthetized cat's nervous system, from spinal cord to cochlear nucleus to olfactory bulb, almost forgetting the original plan to record from awake behaving animals.

Jasper had got wind of the electrode and came down from Montréal to see it for himself and to learn how to make it. It turned out that his group was also working on a system for chronic single-unit recording and had come up with the idea of implanting a hollow screw into the cat's skull, to which the electrode advancer could be attached. The competition got my efforts into focus, as competition often does, and I began to work on an advancer. The problem was not entirely simple. There were no stepping motors then, and a hydraulic system seemed to be the best bet, but one had to make the piston-and-cylinder compatible with a chamber closed to the atmosphere, which was necessary to prevent cortical movements caused by pulsations, as Phil Davies and Vernon Mountcastle had discovered a few years before. I found myself having continually to mollify machinists who were outraged whenever I would come back to them to explain why my latest model, which they had just skillfully built for me, could not possibly work. Finally I decided I must learn how to operate a lathe, and went to night school in downtown Washington, D.C. In the years that followed, the small investment I made in learning machining paid huge dividends, both in equipment and in occupational therapy.

My system worked. The Montréal group, with the help of my electrode, got there first, however, and for a time I wished I hadn't taken so much time recording from so many parts of cats' brains. It has always surprised me how few attempts are made to devise new methods—perhaps it is because one is generally rewarded not for inventing new methods but for the research that results from their use. One's new method is in any case soon modified by someone else whose name then becomes attached to the modified version (I got tired of this happening to the tungsten electrode and, more or less as a joke, began to make electrodes of molybdenum, which is just as stiff as tungsten, confers no electrical advantage, but is a lot more expensive and carries more prestige). I think the time I spent groping around in the nervous system was not wasted even if it delayed my main objective for a few months. The chance to play around at an early stage in one's training is a luxury denied to most beginning graduate students, who often start in on a specialized problem assigned by an advisor, before having a chance to try a few things for themselves.

One day Torsten Wiesel and Ken Brown came over to Walter Reed from the Hopkins Wilmer Institute to find out how to make tungsten electrodes, to try them out in the cat retina. Stephen Kuffler had stopped working on vision some years before but had kept his vision lab going, and Torsten and Ken were collaborating on retinal intracellular recordings. This was my first meeting with Torsten (the electrode turned out to be useless in the retina, because it could not pierce the inner limiting membrane).

I worked with alert cats for the rest of my stay at Walter Reed but abandoned it when Torsten Wiesel and I joined forces, as it became clear that the next steps in studying visual cortex would require eye stabilization. The technique was taken up by Ed Evarts, who adapted it to monkeys at NIH. Evarts' methods ultimately became standard worldwide. My final contribution to the field of chronic microelectrode recording was to adapt the method for depth recording using stereotaxic methods. This allowed me to map the first receptive fields of lateral geniculate cells.

At Walter Reed, in alert animals, I began by focusing on the effects of sleep on cat cerebral cortex. I recorded from striate cortex because there I could hope to identify cells in terms of their specific sensory responses. When I told some of my colleagues that I was going to record from visual cortex they reacted by saying "Why striate cortex? I thought Richard Jung had worked that all out?" That didn't bother me too much: my interest at that point was mainly sleep; vision was a sideline.

Jung and his collaborators were indeed among the world's leading figures in visual cortex physiology, and the only group that had recorded responses from single cells in the visual cortex. They certainly seemed to have everything worked out. Cells fell into four groups which they termed A, B, C, D and E. B-, D- and E-cells responded to one-second diffuse flashes of light at onset, termination and at both onset and termination of the flash. C-cells were inhibited by light. A-cells, strangely, did not respond at all. They were something of a mystery, but the Freiburg group, perhaps because of its interest in epilepsy, regarded them as exerting a dampening or braking effect on cortical activity, as though they existed for the purpose of preventing epileptiform activity.

I quickly confirmed their main results. Stimulating the retinas was easy—the room lights could be turned on and off by pulling on a cord hanging from the ceiling and monitored by a photoelectric cell. I could compare the awake state with sleep, using the EEG to monitor arousal level (REM sleep was still unknown, or had just been discovered).

Jerzy Rose, in one of his visits to Bob Galambos, had made clear to me the importance of histologically monitoring the electrode positions, and luckily Walle Nauta was generous enough to have his technician process my blocks of brain tissue. I had little hope of finding the tracks of these slender wires, much less their tip positions, so I decided to mark tip position by passing current and making lesions. Passing direct current did no harm to the electrode as long as it was made negative, and I estimated how much charge to pass by breaking an egg into a dish, putting the electrode into the egg white and observing its denaturation as current was passed. The first trials, in a real brain rather than an egg, were spectacular, with tiny lesions about 50–100 μm , easily small enough to allow me to tell what cortical layer a cell was in.

One of the first results of using this technique came like a bombshell. One of my lesions, made after recording a B-cell (an on-cell), was in white

matter! The importance of this was that no one had realized that in cortex, extracellular recordings could be made from fibers (probably the exceedingly sharp electrode tip was piercing the myelin sheath). Now one had to consider seriously the possibility that some of Jung's cortical units were myelinated fibers, perhaps including fibers of geniculate origin.

Cell after cell, meanwhile, refused to react to my flashlight or to my pulling the cord that hung from the ceiling light. This certainly confirmed the existence of Jung's A-cells. Thinking that a moving object might have more visual significance than mere light, I began waving my hands in front of the cat. Figure 1 shows the result. One of the cells in this two-unit recording responded to leftward movement, the other to rightward movement (the cat's eyes gave no hint of following the movements—cats soon lose interest and just gaze into space). On another occasion I showed that such cells could respond selectively to up versus down, but for some reason it did not occur to me to try oblique movement. The idea of orientation selectivity was still several years away. These responses to movement were the first indication from a single-cell recording that the cortex might be doing something interesting, something that transcended what the geniculate could do.

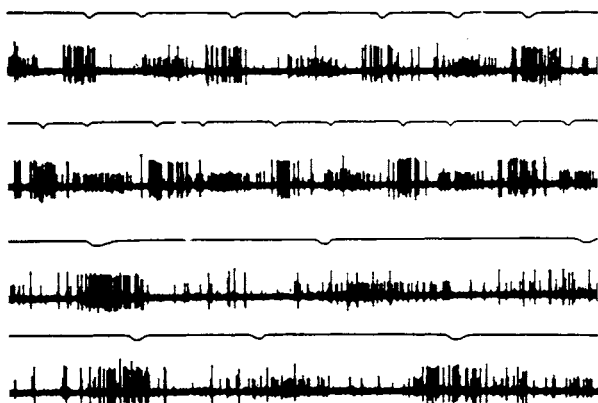


Figure 1. A two-unit recording from area 17 of an awake alert cat showing responses to to-and-fro movements of my hand. One cell responded to left-to-right movement, the other to right-to-left. The upper beam in each of the four traces indicates the movement by deflections produced each time my hand passed in front of a photocell.

I finally became convinced that Jung's A-cells, the ones that had been thought to be unresponsive to visual stimuli and to prevent epilepsy, were actually the cortical cells, the other classes, B, C, D and E, the geniculate inputs. The "unresponsiveness" was a delusion: the cells were unresponsive to changes in diffuse light intensity, not to visual stimuli in general.

The sleep studies meanwhile soon showed that resting activity is profoundly affected by arousal level, and is far more irregular in slow-wave sleep. But I had no way of comparing responses to visual inputs in different arousal states, because the cat slept with its eyes closed. As I saw no easy way of pushing the study further my growing interest in vision took over. Meanwhile, my time at Walter Reed was running out.

I stayed at Walter Reed for a year after my Army service, to get my research to a logical stopping point. Vernon Mountcastle had meanwhile arranged for me to set up a lab in physiology at Hopkins, and the matter seemed to be settled except for the fact that the physiology labs were being remodeled, with an expected delay of about a year from the time of my leaving Walter Reed. One day Steve Kuffler called to ask if I would be interested in coming to his lab to work with Torsten (Ken Brown had left to take a job in San Francisco). That seemed to be a good solution, and a great chance to learn about receptive fields, so I didn't hesitate. I went over to Baltimore one day, and Torsten, Steve and I sat in the lunch room and made plans. It was clear that Torsten and I should try to extend the work Steve had done in the retina to the visual cortex, using the same retinal stimulation techniques that Steve had developed, and adapting my recording methods to acute, anesthetized animals. It was not clear how much the anesthetics might impair the cortical responses, though Mountcastle had shown that somatosensory cortical cells could respond actively provided the anesthesia was kept light.

My family and I moved back to Baltimore in the summer of 1958 and rented an apartment in Rogers Forge, just to the north of the city. By then our oldest child had been born, and Ruth was no longer working. My captain's pay of \$10,000 a year had supported us handsomely and now I had a fellowship that Steve had arranged together with my own R01 NIH research grant and some support from the Air Force. Our row house was clean and comfortable. There are basically two styles of row houses in Baltimore, the old and the newer, and there are a million indistinguishable specimens of each. For this second stint in Baltimore we had the newer type—more comfortable, and fewer cockroaches. Three years before we had lived just five minute's walk from the hospital and socially it was fun as our neighbors were mostly house staff. Now our neighbors were all junior executives, and all were exactly the same brand of Christian (I believe it was Roman Catholic). As Protestant Unitarians we felt like outcasts. It was dull, both socially and architecturally. One night I arrived back in Rogers Forge, parked the car, came up to the front door, and sensed that something was not quite right. The number, 232, was correct, but it took a few seconds to realize that I was at the right house but on the wrong street. That is Baltimore.

Torsten and I wasted no time getting going. It was clear (or so it seemed) that our time was limited to about a year, so we started experi-

menting immediately, using whatever equipment we could scrounge. We began by using the Talbot-Kuffler ophthalmoscope, which restricted us to stimulating one eye, with the cat's head rotated around to face the ceiling. To record we used the advancer I had made for chronic recording, slightly adapted for the acute work. We were recording cells within a week or so of my arrival. I remember coming home one night and saying to Ruth that this collaboration with Torsten was going marvelously well. Our senses of humor and scientific styles seemed to match (or be complementary), and Torsten had wonderful scientific taste, a rock-like solidity and a determination to work on regardless of any roadblocks.

The major breakthrough (to use that hackneyed term) came in our third or fourth experiment. We had isolated a big stable cell which for some hours was unresponsive to anything we did. But as we worked on we began to get vague and inconsistent responses in one region of retina. The ophthalmoscope had been designed for retinal stimulation and recording and was wonderful at generating spots of light of calibrated intensity or dark spots against a light background—but for cortical work it was a horror: it was hard to keep track of where you were in the retina, relative to fovea or disc, and you could only work with one eye. Spots of light were produced by a set of thin wafers the size of microscope slides, made either of brass with holes of various sizes to pass the light or, for black spots, glass slides to which thin metal circles of various sizes had been glued. These wafers, glass or brass, were inserted into a slot in the ophthalmoscope. Stimulus duration was electronically controlled and varied in intensity by a wedge. We struggled, and seemed to be getting nowhere, when suddenly we started to evoke brisk discharges. We finally realized that the discharges had nothing to do with the dark or light spots but were evoked by the action of inserting the glass slide into the slot. The cell was responding to the faint shadow of the edge of the glass moving across the retina, and it soon became clear that the responses occurred only over a limited range of orientations of the edge, with a sharply determined optimum and no response to orientations more than 30 degrees or so from the optimum. We had worked with the cell for about nine hours when we finally stopped for a rest.

This event has sometimes been held up as an example of the importance of "accident" in science. We have never felt that it was an accident. If there is something there to discover one has to take the time to find it, and one has to be relaxed enough about the way one works so as not to foreclose the unexpected. Two other groups failed to discover orientation selectivity because they were too scientific, in a simplistic sense of that word: one group built a device to generate horizontal bright bars, the other group, vertical, in both cases so that they could explore the retina more efficiently than with a roving spot. In a certain

early phase of science a degree of sloppiness can be a huge advantage. We put our care into the electrode advancer, the closed chamber and the electrode itself. We soon replaced the ophthalmoscope, which had been designed for quantitative retinal work, with a screen which the cat could face with both eyes, and a slide projector, and we did not quantify anything about stimulus duration, rate of movement or intensity; we turned the stimulus on and off by putting our hand in front of the projector, and moved the projector by hand. We concentrated on stimulus geometry, which we varied systematically using cardboard, scissors and tape. All these things could have been done electronically or mechanically but at enormous expense in time and money, and with sacrifice in flexibility.

At one early stage, having no proper head holder, we used the head-holder part of Kuffler's ophthalmoscope—the part that had the head facing upwards. Putting a screen on the ceiling seemed awkward, so one day we brought in from home a set of bedsheets which we strung from one to the next of the many pipes that decorated the Wilmer basement ceiling (our lab was about 15 feet square and served also as my office; Torsten had a tiny booth in the next room). One day we were mapping out receptive fields for a three-unit recording, a set of parallel, partly overlapping rectangles which we reached by standing on chairs to get at the sheets; these were cells 3004, 3006 and 3007 in our series, which we began at 3000 to give us a flying start to compete with Vernon Mountcastle, who had just published a paper based on 900 units—when in walked Vernon himself. He was visiting Steve, whose office was just across the hall. We were embarrassed by our slapdash set-up and Vernon must have been horrified. But he was suitably impressed by our three cells, and the implication of the parallel receptive fields of these three neighboring cells for columnar organization of visual cortex cannot have been lost on him. Nor on us! Vernon's discovery of somatosensory columns a few years before was the biggest event in cortical organization since topography, and the possibility that other cortical areas might contain columns was very much on our minds. As he left, Vernon exclaimed to us, "What a great system! You will have your work cut out for you for the next five years". We thought he was being pessimistic. In five years we hoped to have gone on to the auditory system.

Time is strange. Five years in the future can seem like a century, and five years in the past like yesterday. In 1958 neither Torsten nor I could have imagined that 37 years later we would still be working on the same old area 17.

It took a few months before we had enough material to write our first abstract, for *Federation Proceedings* (the Society for Neuroscience was still years in the future). We were both almost paralyzed when it came to writing, and we found that first abstract a real struggle. We gave our first version to

Steve to look over, and I will never forget coming in the next morning and seeing Torsten's face. "I guess Steve didn't think much of our abstract," he said ruefully. Steve's way of criticizing a paper (Figure 2) was like Miss Bradshaw's. He had a passion for clarity and simplicity and a hatred for pompousness.

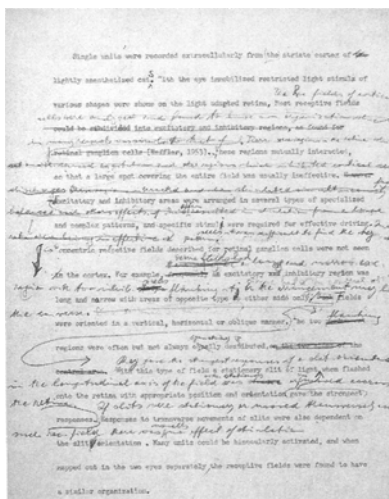


Figure 2. First draft of my first abstract, with Torsten Wiesel, written in the fall of 1958, showing comments by Stephen Kuffler.

From that time on all three of us made a fetish of improving our writing, reading every book we could find on the subject, especially Fowler, Gowers, and Strunk and White. Our entire Wilmer-basement group—Steve Kuffler, Torsten Wiesel, Ed Furshpan, David Potter and later Ed Kravitz—always handed around its manuscripts for everyone to read and tear apart. Torsten's and my first full-length paper, on simple receptive fields, published in 1959 in the *Journal of Physiology*, went through 11 drafts, each a complete overhaul. The acceptance letter, which could only have been written by William Rushton, began "Congratulations upon a very fine paper", and offered no criticisms whatsoever. One has to have known William to realize what a compliment that was.

Shortly after I got to Baltimore, in the early summer of 1958, Furshpan and Potter arrived, having just published their work on the electrical synapse. With Torsten, Steve and I, the five of us formed the nucleus of the group that a few years later became the first department of neurobiology at Harvard. The idea of moving to Boston was concealed from me until very late. Torsten would often say that we had to hurry up with our work because our time was limited, but I could never understand why: my moving to a lab two blocks away should hardly preclude our continuing to collaborate. One day while driving me home, Steve casually

asked how deeply committed I was to going over to physiology. Would I consider moving to Boston with him, Torsten, Ed and David? I had had no inkling that any exodus was in the air until that moment. It didn't take long to decide; our work was going too well to break it off at that point, and though Boston was a complete unknown, the move sounded like an adventure. Ruth and I had come to like Baltimore, and had even made an offer on a house. Luckily that fell through, or we might never have left.

That spring nine families made the migration. Our family, then four (Carl was born at Walter Reed, Eric in Baltimore), rented an apartment for the first year in Newtonville. Harvard, especially the senior faculty, seemed ponderous compared with Hopkins which had been informal and friendly; at Harvard only full professors dared to speak at faculty meetings and the speeches were more like orations. For the first few years our group was lodged within the department of pharmacology, and we grew steadily. Torsten and I had no great security: we had been made assistant professors at Hopkins, but were demoted to the curious rank of associate when we went to Harvard. On the other hand this was just the beginning of NIH extramural support for medical research, and we immediately got grants of about \$10,000 a year—a lavish amount in those days. In any case, proposals took about two days to write. One feels not at all envious of young people starting out today, with support so much harder to get and keep, grant writing consuming months, and our field so much more crowded. In 1960 it could not have been less crowded; we virtually had the visual cortex to ourselves. If we had doubts about a paper, its contents, language or its excitement, we could put it in a drawer and think about it for a while.

In the early 1960s we began a pilot project on visual deprivation by sewing closed one eye of a few kittens. Torsten recalls our standing in the hall discussing what we should do. He suggested bringing up the animals from birth in the dark. I said that that sounded like a real bore; why not simply sew closed one eye and have the other one as a control (this is his version; I don't remember the discussion at all)? We went ahead, sewed the lids, and a few months later were astounded at the magnitude of the changes in responsiveness of cortical cells to stimulating the closed eye. We were lucky; had the fall-off in responses been subtle, requiring, for example, quantification, we surely would not have gone on with the study. But it took off and led to years of work. It was years before we wrote a grant request for this work, which was done strictly on the side, and cost nothing, because the kittens were all bred from lab cats. Cats, in any case, cost only a few dollars each, compared to about \$400 today. Animal rights groups were then only a vague cloud on the horizon.

Our work continued to develop, extending to the lateral geniculate, to visual area II, to what we called area 19 in the cat and to the Clare-Bishop (lateral suprasylvian) area; to color, stereopsis and to monkeys. One day Jim Sprague wrote from Philadelphia to say that one of his technicians, Jane

Chen, had for personal reasons to move to Boston. Jane was expert in the Nauta method for staining degenerating fibers. Could we use her? We debated. We had a small histology lab which we used to cut and stain sections to identify electrode tracks and to look at geniculates of deprived animals, but we were not anatomists, and we didn't want to make fools of ourselves. But the chance seemed too good to be missed, and Jane became part of our enterprise. Anatomy and physiology were very much separated then. Housed in separate departments, anatomists almost never did physiology, and we, as physiologists, were unusual in even looking for our electrode tracks (the big exception was the Hopkins group, where the two fields were far more allied: I have already mentioned Rose's urging me to do anatomy).

In our recordings we had just caught on to the existence of ocular dominance columns, first in cats and then in monkeys, and we thought it would be exciting to identify these anatomically. Our first anatomical foray was to use our electrodes to make tiny lesions in regions the locations of which we could identify by recording. We tried this first in single geniculate layers, and it led immediately to a huge payoff: we could stain the degenerating fibers with the Nauta method, reconstruct the columns in serial cortical sections (in area 17 of monkeys), and show that geniculate afferents ended not in the Line of Gennari, as had been supposed, but mainly in what came to be known as layer 4C, just below the Gennari Line. More than that, the input was tripartite, with magnocellular layers projecting to the upper half of 4C and the parvocellular to the lower half and to 4A. All this seemed like a gift from the gods. We had no credentials for doing anatomy, much less for working in one of the most formidably difficult techniques of that era. Of course, we just made the lesions and looked at the slides: Jane was the expert.

Later we came to use radioactive tracers to answer the same questions. Bernice Grafstein had shown that when injected into an eye a tracer could be shown by scintillation counting to have reached the cortex, having somehow traversed the geniculate. It occurred to us that if we could demonstrate this autoradiographically we would be able to see the entire system of columns. We tried, but with no success. Luckily, at about that time I went to Madison, Wisconsin, to give a seminar in Ray Guillery's lab, and noticed that they were looking at all their autoradiographs under dark field. I returned to Boston, told Torsten, we put a slide under dark field, and there were the columns in all their glory. I decided that sometimes trips are not a waste of time.

Our science seemed not to conform to the science that we are taught in high school, with its laws, hypotheses, experimental verification, generalizations and so on. We felt like 15th century explorers, like Columbus sailing West to see what he might find. If we had any "hypothesis" it was the simple-minded idea that the brain, in particular the cerebral cortex, with all its ordered complexity, must be doing something biologically meaningful with the information that comes into it—that what came out must be more elabo-

rate (for want of a better word) than what went in. So we recorded cells to see what we could find. I suspect that much of science, especially biological science, is primarily exploratory in this sense. Those who think that "Science is Measurement" should search Darwin's works for numbers and equations.

The freedom that the system of science administration offered in the 1960s and 1970s was marvelous. One could change one's program of experiments at a day's notice without informing (much less getting permission from) a department head or funding agency or animal committee; no one seemed to care about close correspondence between what you said you would do in a grant proposal and what you actually did. You did not need to have the work practically completed to get it funded. Numbers of papers were presumably counted by deans, but we largely ignored any pressure that might have existed to publish. We felt gratified if we wrote a paper about once a year, and we often combined two or three papers into one big paper if it seemed to make esthetic sense. We were not alone in this. Ed Furshpan could easily take the prize for substance-to-quantity-of-papers ratio, for some years, averaging one totally new synapse per paper.

We had similar feelings about numbers of students and postdocs in our labs. First, it seemed to us that in an entire career, if one contributed to the training of three or four first-rate scientists, one was doing well. Luckily for us, experiments in integrative neuroscience are generally done by the scientists, not by armies of technicians or graduate students, as is the case in molecular biology, so students, though fun and intellectually stimulating, were not a necessity for our own work. Second, we felt that independence is crucially important for training in science—that when you hand young people a problem to work on you may be depriving them of the most important learning experience, namely that of choosing a problem. It seems far better to flounder around for a while, trying one thing after another and finding out what kinds of science suit you, than to be presented with something someone else thought up. Graduate students or postdocs in our group certainly felt neglected, and they complained—Jim Hudspeth, one of the very best, complained the loudest—but I think the policy paid off in the quality of the people we trained (if "trained" is the right word). We learned as much from them as they did from us.

Our attitude toward training was probably to some extent copied from Steve, who never urged us to do or not to do something. At most, he would look bewildered when an idea or result of ours made no sense, or was not clearly described. He did, at the start, urge us strongly to measure and specify such things as the brightness of our stimuli and backgrounds, saying that no one would believe our results unless we put in a few numbers. We put them in, but looked on it as politics more than science. Steve's main influence on Torsten and me was by example. He did an experiment roughly every day, and he did virtually everything himself—dissections, recordings, writing the papers. When he collaborated, he and his co-worker

took turns at the various jobs: dissections, writing papers and so on. This was our style too; for a short time we had a technician tidy up our lab but we discovered that it took her two hours compared to our 10 minutes, and then we could never find anything.

So we had technicians cut and stain histological sections, which we were never tempted to learn how to do. Above all we discovered that in an experiment three is a crowd, and we almost always worked by ourselves. The exception was a most productive collaboration with Simon LeVay in which the work was rather cleanly divided into anatomy and physiology. Obviously in these things one's style has to be fitted to the science, and I assume that there are good reasons for the 46 collaborators and co-authors in a high-energy physics paper. One can understand, but not envy.

There was a slack period of a few years, in the 1970s, when we attempted an exploration of the region of pre-striate cortex that is bounded by and includes that horror of complexity, the lunate gyrus. We recorded from a few hundred cells from each of two areas, which are now termed 3A and MT. But at that time everything north of 18 was called "19" and we thought (wrongly) that the first area might be area 18 (visual II), and (rightly) that the second might be the analog of the cat Clare-Bishop area. The first (3A) was packed with stereoscopic-depth sensitive cells, but we backed away from writing up the results because we did not know what to call the area. The second (MT) we thought was boring (again, wrongly!) because it was so similar to the Clare-Bishop. We were premature in this undertaking, since what was needed at the time was a working out of the topography of pre-striate areas, as Allman, Kaas, Zeki and Van Essen subsequently did. We had no patience for this, gave the whole thing up and obeyed our inclinations by returning to our old familiar area 17, concentrating on the orientation and ocular dominance columns, hypercolumns and magnification and modules. Now, 25 years later, one has what are possibly reliable topographic maps of one or two dozen pre-striate areas the physiology of which is ripe for exploration. To work out the striate cortex has taken decades, and these various pre-striate areas are already turning out to be just as complicated and interesting. I find today's rate of progress disappointing, however. Monkeys cost a fortune, and the present popular mode of working with awake behaving animals, fertile as it is, seems ill-suited for the anatomically oriented physiology that is needed, grueling though that sometimes is.

One of the most pleasing advances came to us not during an experiment, but in the course of writing a paper. We had found, in the first year or so of work, that the cells in the visual cortex differ in the complexity of their behavior, forming a hierarchical sequence. Its members we termed "simple", "complex" and "hypercomplex". Cells at each level were presumed to receive their input from cells at the preceding level. These cell types were first found in the cat, and later, with some differences, in mon-

keys. The idea that the orientation columns must have the function of housing together sets of cells that the physiology—the circuits subserving the hierarchy—has shown must be interconnected, seemed to us to be one of the most deeply and aesthetically pleasing ideas of a lifetime.

We of course expected to be able to extend this hierarchy to cells of higher and higher order, and I suppose that was largely why we took on the pre-striate areas. To our surprise the quest was not very successful. Today it seems likely that our failure to find more and more complexity related to form perception has to do with the presence of other complicating dimensions of vision that also have to be dealt with by the brain. In plowing ahead we stumbled on two such areas, one concerned (at least partly) with stereopsis, the other with motion, and neither perhaps primarily concerned with shape. The advantage of working in the striate cortex, and also in V-2, was that at these early levels all the submodalities (form, color, movement, depth) are represented, in different layers or as mosaics of stripes or blobs. In the pre-striate areas we were probably not lucky enough to look in the right places. For form analysis, the best place to look would have been area V-4, or the temporal lobe.

It sometimes seems to me that the sedulous nature of our work has been exaggerated, perhaps with intent to flatter, with adjectives like tedious, painstaking, careful, even plodding. But there must be few fields in science in which at the end of a day (perhaps a long day!), you can say that you have really found something new and unexpected. That may not happen every day, but it has not been rare. Examples, in no special order, are the discovery of color cells in blobs, end-stopping, the way geniculate cells enhance the antagonism of receptive field surrounds, color-spatial relationships in geniculate cells, orientation columns, direction selectivity, the scrambled topography of cortex in Siamese cats, the scrambled order of fibers in the optic nerve, the midline representation of the corpus callosum, the absence of sharply defined ocular dominance columns in newborn monkeys, the milder effects of binocular deprivation compared with monocular and the splitting up of binocular inputs as a result of strabismus. Most of these things became evident in the course of a day, more or less, and the sheer excitement is hard to convey. There were of course tough days too, in which nothing seemed to work. I can hear Torsten exclaiming, "Why is everything so difficult?" There were late nights when I knew we should quit when Torsten began to talk in Swedish.

When in 1981 Torsten and I won the Nobel Prize for all this work, the immense pleasure of the award (and the week-long party in Stockholm) was tempered (only slightly) by the worry that we might never be able to work again, at least not at the same pace. Mail, administration and invitations to give talks or receive honorary degrees would consume us. By and large that has not been so, at least not to the extent that I had feared. It had already become harder for us to collaborate by the late 1970s

because of increased pressures of many kinds, and finally we had to split, Torsten beginning a collaboration with Charles Gilbert and I with Marge Livingstone. For two 60-year-old guys to continue to work at the pace of postdoctoral fellows and answer the mail and write letters of recommendation and be on committees was to expect too much.

The work with Marge has continued to be exciting. The first two years we spent recording from the cytochrome oxidase blobs and showing their involvement in color mechanisms, and in examining the physiology of the three kinds of stripes into which area 18 (now called V-2) is divided. We became increasingly intrigued by the separation of pathways into branches involved in form, stereopsis, movement and color, and in the striking tendency for these submodalities of vision to be independent of one another perceptually. We got into deep trouble over this foray into psychophysics, a field that has been late in integrating with the rest of neurobiology. But it is understandable that experts in a field that is hundreds of years old and rather sophisticated should object to the methods and ideas of those whom they must have looked on as bulls in a china shop. It was fun, instructive, and gratifying (in a way) to go through a period in which half the papers in neurobiology (it seemed) were aimed at proving our results wrong.

Marge and I have now gone over completely to working in awake behaving monkeys, in my case because after 35 years of mapping receptive fields until well beyond the Late Night with David Letterman Show, I was ready for a change. But I do regret abandoning the struggle to work out cortical organization, which requires a combined anatomy-physiology approach and accurate reconstruction of electrode tracks that is hard to do in animals that are kept around for many months.

Neurobiology did not exist when I started. It was great fun seeing it spring up at the time the departmental barriers separating its components—atomy, physiology, chemistry and experimental psychology—were broken down. Scientifically we are in a far stronger, healthier state, threatened only by the possible failure of society to keep up the expensive business of supporting us. I hope that does not happen!

Selected Publications

- (with Wiesel TN) Receptive fields of single neurones in the cat's striate cortex. *J Physiol* 1959;148:574–591.
- (with Wiesel TN) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J Physiol* 1962;160:106–154.
- (with Wiesel TN) Receptive fields and functional architecture of monkey striate

cortex. *J Physiol* 1968;195:215–243.

Evolution of ideas on the primary visual cortex, 1955–1978: A biased historical account. (Nobel lecture.) *Biosci Rep* 1982;2:435–469.

Eye, brain and vision. Scientific American Library, No. 22. New York: WH Freeman, 1987.

(with Livingstone MS) Connections between layer 4B of area 17 and the thick cytochrome oxidase stripes of area 18 in the squirrel monkey. *J Neurosci* 1987;7:3371–3377.

(with Livingstone MS) Segregation of form, color and stereopsis in primate area 18. *J Neurosci* 1987;7:3378–3415.

(with Livingstone MS) Psychophysical evidence for separate channels for the perception of form, color, movement and depth. *J Neurosci* 1987;7:3416–3468.

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