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Dale Purves

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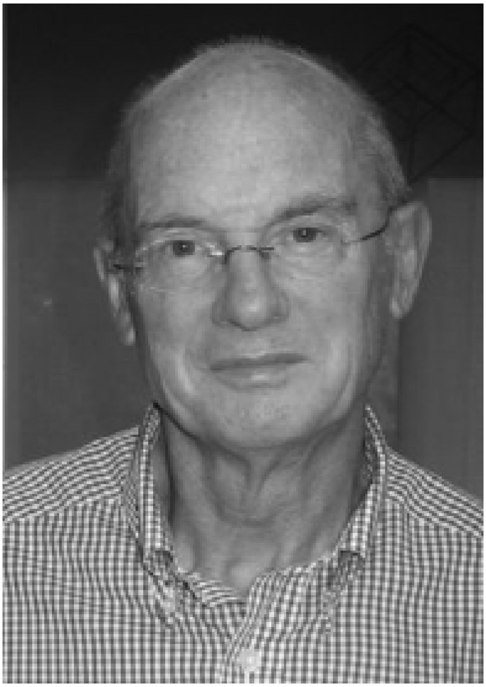

Dale Purves

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Intern in Surgery, Massachusetts General Hospital (1964–1965)
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Alexander Forbes Lectures, Grass Foundation, MBL (1983)
Camillo Golgi Award Lecture (FIDIA) (1988–1989)
Election to National Academy of Sciences (1989)
Grass Lecture, Society for Neuroscience (1990)
Lezioni Lincee Award Lectures, Accademia Nazionale dei Lincei, Italy (1992)
Election to the Institute of Medicine (1996)
Election to the American Academy of Arts and Sciences (1999)

Although Dale Purves is known for his earlier work on neural development and synaptic plasticity, his research during the last 20 years has sought to explain why we see and hear what we do, focusing on the visual perception of lightness, color, form, and motion, and the auditory perception of music and speech. The goal of this work has been to establish an operating principle for nervous systems based on the fact that sensory systems cannot measure physical reality directly and therefore must use accumulated experience to generate the basic qualities we perceive. This understanding of neural function runs counter to the widely held view that sensory information is used to compute models of reality.

Dale Purves

Childhood

I was born in 1938, the second child and first son of an upper middle-class Philadelphia family. My long-suffering father was a businessman saddled with an impossibly neurotic wife and four children who were in various ways a difficult lot. Although successful in business, he was deeply interested in science, math, and music.

My father's burdens were not made any lighter by me. As a young child I was a mess, refusing to go to preschool and throwing tantrums at the prospect of social engagements. There were attempts to establish a diagnosis and as a four- or five-year-old I remember seeing a psychiatrist. Nothing came of this effort and by first grade I seemed to be coming around. Further restoration to relative normalcy came when my father, at the age of 45, resigned his vice presidency at the Stetson Hat Company and took a job setting to rights a steel company in Mexico City at the behest of a New York financier. Our new lives in Mexico turned me from a cranky kid into a more or less typical neighborhood boy who was good at tops, marbles, yo-yos, and sports and who played with five or six local children on the unpaved street in front of our house. As a second grader, I quickly learned Spanish and was a good and enthusiastic student at the bilingual school I attended. Adding to this time of general contentment was my father's enthusiasm for wide-ranging travels in Mexico. These halcyon days came to an end, however, when my dad was fired for siding too often with the Mexican workers rather than management (he was a small "d" democrat through and through). We returned to Philadelphia in 1949, where I rejoined my class at the Germantown Friends School at the end of fifth grade.

Anxiety about my father's new job as a founding partner of a management consultant firm was palpable. Adding to his worries my mother had a "nervous breakdown" and left for the Institute of Living in Hartford where she stayed for several months. I soon turned into a worrisome teenager given to periods of depression, general misbehavior, and grades that reflected all this. The saving grace was the very good school I attended, a group of new friends, and the gradual realization that science was interesting. Having no concept of scientific practice outside the classroom, I gravitated toward medicine as a profession that might mix science, excitement, financial reward, and social status. To test these waters, when I was 16 or 17, I spent the summer living with my aunt and uncle in Connecticut working as an orderly in the local hospital. Despite emptying bedpans, shaving male abdomens in preparation for surgery, and cleaning up after the occasional autopsy, the ambience of medicine was appealing. The obvious respect of patients and nurses for the doctors encouraged the sense that medicine was a good bet. And my high school courses in chemistry and physics under an excellent teacher began to restore my academic credibility. It was soon clear that I would head to college as a premed student.

College

When it came to choosing a college, I gave the issue very little thought. My father, presumably having seen too many Princeton products in Philadelphia society, indicated that if this was my choice, I would have to pay my way. That left Harvard and Yale. Harvard had a reputation for being effete and Yale appealed to me as more "manly." My ignorance about what would be facing me and my unsuitability for playing the proverbial Jack Armstrong All American Boy role was profound.

When I matriculated at Yale in the fall of 1956, I quickly discovered some unhappy consequences of my choice. My class of about 1,000 was frontloaded with young men (it was a decade before women were admitted) from New England prep schools who knew the ropes and came with a cohort of friends (or at least knew who their enemies were). I knew no one. In my zeal to "belong" at Yale, I had indicated on my application I would just as soon have WASP roommates. As a reward, I was assigned two lily white Protestants with whom I had nothing in common and one of whom was patently weird. Things got worse when my high school girlfriend at the time, a first-year student at Mount Holyoke, unceremoniously dumped me. I was also brought up short by a failing grade on my first chemistry test. None of this helped my mental status. I should have sought counseling but did not want to be "stigmatized." The final straw in my comeuppance at Yale was "rushing" a fraternity only be turned down despite family connections. Having failed miserably in my misguided effort to become a proper Yale man, I told my father that I was quitting college to join the Army. He convinced me over a somber lunch at the Century Club in New York (to which he had been recently been elected) that this was not a good idea. Although his new club was not the best locus for the meeting, perhaps the subtext was that if he could succeed after being fired in Mexico, I should not quit so easily. Thoroughly beaten, I returned to New Haven.

The aspect of Yale that had little of my attention in high school—its academic excellence—eventually began to sink in. Although I had failed my first test in freshman chemistry, I had buckled down and ended the semester with the top grade. Deciding to work hard (I was a premed after all) was the first sensible choice I made at Yale. The second was to major in philosophy. I had a knack for thinking more or less logically and my philosophy professors seemed to recognize that they'd hooked a live one. By the time I was a rising junior, I had become a committed intellectual and by the end of my junior year, my early failures had dimmed, although they certainly were not forgotten. In the end, I graduated 1 of 15 students awarded a degree *summa cum laude*. The most important thing I had learned at Yale, however, was that I was capable of incredible stupidity at an age when I should have understood myself and the world better. When it came time to apply to medical school, I gave the matter more thought than I had given what college to attend, but it didn't take much investigation to recognize that Harvard topped the list. I applied for early admission and was accepted with the idea that, given my interest in philosophy, psychiatry might be a good specialty for me.

Medical School

Although "enjoyable" is not the right adjective to describe medical school, I felt for the first time that I was in the right place with the right colleagues and the right teachers doing something serious. Given my potential interest in psychiatry, I was especially attuned to what I might get out of our first-year course on the nervous system. I assumed it would be the beginning of a new effort to learn about brain biology in a more serious way than I had managed as an undergraduate, and so it was. The senior member of the neuroscience teaching faculty was Stephen Kuffler, then in his early 50s and already a central figure in neuroscience. Having recently arrived at Harvard from Johns Hopkins, he had presciently promoted to faculty status two postdoctoral fellows who had been working with him, David Hubel and Torsten Wiesel. They were then 34 and 36, respectively. He had also hired David Potter and Ed Furshpan, two even younger neuroscientists who had recently finished fellowships in Bernard Katz's lab at University College London. The last of his initial recruits was Ed Kravitz, who at 31 had just gotten his doctorate in biochemistry from the University of Michigan. Furshpan and Potter taught us how nerve cell signaling worked, Kravitz taught us neurochemistry, and Hubel and Wiesel taught us about the organization of the brain (or at least the visual part of it, which was their bailiwick). Kuffler gave a pro forma lecture or two, but teaching was not his strong suit and he had the good sense to let his new young faculty carry the load.

Unlike teaching us about nerve cells and the mechanisms of the action potential and synaptic transmission, conveying some idea of what the brain is actually doing was a difficult task in 1961. Hubel and Wiesel dealt with this challenge by simply telling us about their work on the organization and function of the visual part of brain. It was not unusual for professors to cop out by telling us what they had been doing in their labs rather going to the effort of putting together a broader and more useful introduction to some subject. But in this case, it was obvious that what Hubel and Wiesel were trying to do was extraordinary. Based on what Kuffler had established in the retina, they were exploring the properties of visual neurons in progressively higher stations in the visual system of the cat, and this was the work that we students heard about as an introduction to the brain.

Despite the excellence of these extraordinary teachers, much of what I had learned from them was soon forgotten. It was not lost on me, however, that the group Kuffler had put together represented a remarkable collection of scientists working on problems that were importantly connected to my conception of what I might eventually do. But all of us had to cope with the courses or rotations that were coming next, and I was still wedded to the idea of pursuing psychiatry.

Disillusion with Psychiatry

My conviction that psychiatry was a good choice began to wane as my knowledge of the field waxed over the next few years. The first disillusion came during the summer after my first year in medical school, not long after the course that Kuffler and his recruits had given us. There was a summer break between first and second year, and we were encouraged to spend the summer working in one of the research labs at the school. Our pharmacology course during the first year included several lectures on psychoactive drugs and, given my inclination toward psychiatry, I thought working with the professor who had presented this material made sense. But the only significant result by the end of my research summer was the demise of an unconscionable number of rabbits.

The experience that disabused me once and for all about the merits of pursuing psychiatry, however, was my first clinical rotation. Although we had some instruction in psychiatric diseases during the second year of medical school, our exposure to the psychiatry wards did not come until the third year. My rotation in clinical psychiatry was at the Massachusetts Mental Health Center, housed in a ramshackle building a few blocks from the medical school. Psychiatry at Harvard in 1963, and at the Mass Mental Health Center in particular, was one of the last strongholds of the Freudian analytical treatment of severely disturbed patients, and the preceptor during my rotation was a psychiatrist who believed strongly in this concept. Sitting through his psychoanalytically based interrogatories of psychotic patients eroded what little remaining faith I had that psychiatry was the field for me. The final blow came one Saturday afternoon when another student and I found a patient who had hung himself in one of the bathrooms. The usual resuscitative procedures were far too late to help, but the psychiatry resident in charge seemed to have less knowledge about how to proceed than we did. The message was clear: psychiatrists were not real doctors, and being a real doctor loomed large for me.

Surgery

Anyone navigating the rigors of medical school gravitates toward one or more role models to provide inspiration and, having given up on psychiatry, I began to look elsewhere. Harvard abounded in potential models and one of most charismatic was Francis Moore, the chief of surgery at the Peter Bent

Brigham Hospital, where I did my third-year rotation in surgery. Moore was then in his early fifties and already legendary. As an undergraduate at Harvard, he had been president of both the Harvard Lampoon and the Hasty Pudding Club, and was appointed surgical chief at the Brigham at the age of 32. He was a member of the team that had performed the first successful organ transplant in 1954 and had written a widely respected book in 1959 called *The Metabolic Care of the Surgical Patient* that underscored his status as a physician-scientist. Holding retractors as a student assistant while Moore exercised his jocular authority and surgical skills turned me in a new direction. I decided then and there that I would train in general surgery.

After some further electives in surgery during my last year in medical school, I applied for a residency in general surgery at the Massachusetts General Hospital, then considered the top program despite Moore's preeminence at the Brigham. I was accepted and started my surgical internship in the summer of 1964. It is hard to believe in today's atmosphere of managed care, oversight by insurance companies, and litigation that we "doctors in training" were largely unsupervised. The wards were always filled with patients who could not afford a private doctor, and for better or worse, they were entirely our responsibility ("better" was around-the-clock care by dedicated young doctors; "worse" was our lack of experience).

The chief resident I worked under during the first part of my internship year was Judah Folkman. Like Moore at the same age, Folkman was thought to be destined for great things, as turned out to be the case. At 34, Folkman was named surgeon-in-chief at Boston's Children's Hospital, becoming along with Moore one of the youngest professors ever appointed at Harvard Medical School. He became justly famous in the early 1970s for pioneering a novel way of treating cancer by inhibiting blood vessel growth, and at 46, he gave up this appointment as a professor of surgery to pursue basic research on angiogenesis. Folkman was perhaps the most impressive individual I had ever met. Physically slight, already balding, with a great beak of a nose, he dominated in any setting by intelligence, wit, and force of character. The residents universally looked up to him not simply because he was surgically skilled and supremely smart, but because he radiated confidence and integrity that made everyone under him deal better with the daily strife and our inevitable mistakes.

For me, however, working under Folkman that year had another effect. Any competitive individual continually measures himself or herself against the qualities and talents of peers. Although as chief resident Folkman was far advanced from an intern struggling to learn the rudiments of the trade, he was only five years ahead of me, and I had to envision myself in his role in the near future. The comparison was discouraging. I didn't see him as necessarily smarter or feel that I could never reach his level of technical skill (although I had serious doubts on both counts). What dismayed me was his obvious passion for the craft, which I had already begun to realize I lacked. The recognition that, like psychiatry, a life in general surgery was probably not my calling came at 2 or 3 in the morning when Folkman was trying to make an apparatus to dialyze a patient dying from kidney failure using an old washing machine and other odds and ends he had collected from a hospital storeroom. Although the effort failed, I realized that I would not have made it and that this disqualified me from trying to follow the footsteps of figures like Folkman and Moore.

Venezuela

Thus, I needed to invent another path to the future. This time I was given some breathing room by the war in Vietnam. By 1965, virtually all physicians in training were drafted, and my notice arrived about halfway through my internship. Given my concern over the prospects of a career as a general surgeon, being drafted was not entirely unwelcome. There was another reason as well. Since childhood I had suffered periods of depression. A year of psychoanalysis during my last year of med school had not helped, although it confirmed my conviction that psychiatry was not something I wanted to pursue. I ended my internship year without a clear plan and clinically depressed. The bright side was that I would now have two years of enforced service to pull myself together and sort things out.

Despite the rapidly escalating war in Vietnam, the options for physicians drafted in 1965 were still broad. I could join one of the armed services; seek deferment for further surgical training; apply for a research position at the National Institutes of Health; join the Indian Health Service; or apply to become a Peace Corps physician. This last option meant serving two years in the Public Health Service taking care of Peace Corps volunteers in one of many countries around the world. Given my uncertain frame of mind about what to do next, my total lack of interest in research, and my opposition (along with almost everyone else I knew) to the war, the Peace Corps seemed the best bet. And so, after a few weeks of remedial training in tropical medicine at the Centers for Disease Control in Atlanta, I arrived in Venezuela in July 1965.

As it turned out, the Peace Corps was a good choice. The volunteers that I and another young doctor had to look after were an inspiring bunch who demonstrated all the good things about Americans and American democracy of that era. Since I spoke Spanish as the result of living in Mexico as a kid, I could travel easily and interact well with local doctors. And Venezuela in the 1960s was a beautiful, prosperous, and relatively progressive country. From the medical perspective, the job was easy, serving as general practitioner to about 400 sometimes difficult to reach but generally interesting and healthy young adults. My life in South America was in every way a radical change, and for the first time since college, I had time to think rather than simply meet the demands of medical training.

I read widely, including a lot of books on science that I had not been exposed to as an undergraduate majoring in philosophy or as a medical student and intern with no spare time. One of the books I picked up while rummaging around the American Bookstore in Caracas was *The Machinery of the Brain* by Dean Wooldridge. Having become wealthy in the aerospace industry, Wooldridge had resigned in 1962 to pursue his passion for basic science. *The Machinery of the Brain*, published in 1963, was his first effort. Although I was passingly familiar with much of the content, his lucid synthesis of the information I had learned about the brain as a med student got me thinking about issues that I had been keenly interested in but had lost touch with as a prospective surgeon. Wooldridge's book was modest and provocative and got me thinking about the nervous system once again.

Because I had two years to mull things over before I was scheduled to resume my post as a resident in general surgery at Mass General, there was no rush to sort out my thoughts about a career that might combine an interest in the brain with my training as a physician. I eventually concluded that the most logical course under the circumstances was neurosurgery. In addition to the internship year I had already completed, becoming a neurosurgeon required another year of general surgery that awaited me on my return to Boston, so I was already well along this path. Neurosurgery, I thought, would combine my earlier and now reviving interest in the nervous system, which I had pushed aside as a result of my disillusion with psychiatry.

And so, soon after returning to Boston in the summer of 1967, I asked William Sweet, the head of neurosurgery at Mass General, if I could join his program when I completed my second year of general surgery. He agreed, and I was thus to start formal training in neurosurgery the next year. Despite the logic of this plan, within a few months of my return from the Peace Corps, I began to have doubts about what had seemed, in principle, a good marriage of interests and training up to that point. Sweet was no Francis Moore or Judah Folkman, and his colleagues on the neurosurgery faculty at the time were not much more inspiring. In fact, what they did on a daily basis was not, when I experienced it firsthand, all that interesting. In contrast to my abstract enthusiasm for exploring the brain, the actual operations were long and tedious, and the outcomes all too often a foregone and unhappy conclusion.

As I worried increasingly about the prospect of neurosurgery, my thoughts kept turning back to the young neurobiologists Kuffler had brought to Harvard in the late 1950s and the impression they had made on me. Thus, in the winter of 1967, I found myself back at Harvard Medical School in the office of David Potter, who had taught us about action potentials and synaptic transmission six years earlier. I remembered Potter as the most approachable of the group and sought him out for advice about whether research in neuroscience might be a reasonable option. He listened with apparent interest as I summarized my concerns with neurosurgery and my interest in perhaps giving research in neuroscience a try. On the face of it, my arguments were feeble: the sum total of my research experience was the disastrous summer spent in a pharmacology lab, and my desire to try research had been reached largely by excluding other options. Despite the weakness of my case, Potter said he would think about my situation, and we agreed to meet again. In the meantime, I asked Sweet if I might take my first year in the neurosurgery program as a research fellow, and, primarily because of scheduling issues, he agreed.

When I returned to Potter's office a couple of weeks later, he considered my intention to try research plausible enough, and suggested that I contact John Nicholls to see if he could take me on as a fellow. Nicholls was working at Yale as an assistant professor and had just been recruited to Harvard by Kuffler. I was disappointed because I had no idea who Nicholls was and had hoped to work with Potter himself or perhaps Hubel and Wiesel. I was even more dismayed when Potter told me that Nicholls was working on the nervous system of the leech. I had no idea what any of the neurobiology faculty was doing then or why, but it was difficult to imagine how the leech was pertinent to my ill-formed ambition to become a neuroscientist.

In fact, the suggestion was a good one. I was somewhat reassured when Potter told me that Nicholls had been a graduate student with Bernard Katz in the late 1950s after he had completed his medical training in London; that he had been a fellow in Kuffler's lab thereafter; and that his work on the leech was widely regarded as an outstanding example of what was then a new approach to understanding neural function—namely, studying the nervous systems of simple invertebrates. More to the point, Potter went on to say that because Nicholls would be starting up a new lab at Harvard, he would probably welcome a fellow, even one whose experience in neuroscience was nil. Thus, I wrote to John who invited me to visit him at Yale.

And so on a bleak Saturday in February 1968, Shannon Ravenel, whom I was engaged to marry later that spring, and I drove down to New Haven. I had met Shannon, an up and coming editor at Houghton Mifflin, while still in med school and we had had an on-again off-again relationship that, happily for me, had been on-again since I returned from Venezuela. Yale Medical School was unimpressive (I had never actually been there, even though it was only a few blocks from the residential college where I had lived as an undergraduate). John's lab was equally nondescript, and it was quickly evident that John himself had a complex personality that might not be a good fit with my own. Driving back to Boston that night, Shannon pointedly asked me if I really wanted to make this change in the light of all the evidence that I would be sailing into uncharted waters. Even though my confidence in answering was minimal, there were several reasons that argued for seeing it through: Potter's word that Nicholls was a good mentor; the lack of obvious options if I wanted to try research; and a determination on my part to do something that might ignite a passion for understanding the brain. And I could always go back to the neurosurgery program at Mass General if the research year failed. Thus, a few days after getting back to Boston, I called John to say that I was willing if he was. Shannon and I married in May, I finished my year of residency in June, and after spending that summer in Vietnam under the auspices of a Boston-based antiwar group selecting war-injured children for treatment in the United States, at age 30, I began my life as a neuroscientist.

Postdoc at Harvard

Although the Department of Neurobiology at Harvard was probably the best place I could have tested the merits of this new choice, the transition was not easy. For the previous four years, I had been a practicing doctor: whether in Boston, Venezuela, or Vietnam, I had had all the responsibilities and respect that being a physician entails. Suddenly, I was a superannuated student on the bottom rung of the ladder; even the two beginning graduate students in the department knew much more science than I did, and they seemed a lot smarter to boot. The stress was of a very different kind than I had experienced during the years I had worked in surgery, but the first year I spent in John's lab was nearly as trying. There was, however, a fundamental difference: despite my ignorance and well-justified sense of inferiority, I finally loved what I was doing. For the first time in years, I worked hard not because I had to, but because I wanted to.

The approaches to the brain and neural function that Kuffler and his young faculty were spearheading when I was a student in 1961 had flowered by the time I returned as a fellow in 1968. The question that always confronts the next generation of scientists—Nicholls and the rest of the faculty in this case—was what to go after next. One answer to the question had already been supplied by Kuffler's study of the retinal cell responses at Hopkins, the impetus for the work on vision being carried on by David Hubel and Torsten Wiesel. By the time I arrived back at Harvard as a fellow, they were already well on the way to the dominant position in brain physiology that they would hold for the next several decades. Another aspect of Kuffler's work had stimulated a quite different direction that seemed equally promising, and this had determined the work John Nicholls was doing when I joined his lab. Following his graduate work with Katz, John had joined Kuffler's lab as a fellow in 1962, and they had worked together to understand the function of glial cells using the leech nervous system as a model. By the time John left Harvard to join the faculty at Yale, the work on glia had finished, but he continued using the leech as a simple system in which to explore neuronal circuitry in relation to behavior. The opinion held by Nicholls and many other neuroscientists when I joined his lab in the fall of 1968 was that a logical next step in moving beyond the established understanding of neural signaling would be to focus on invertebrate nervous systems to fathom basic principles of neural function. The prospect of relating the function of identified nerve cells to some bit of behavior was attractive and that was the topic I threw myself into as a novice neuroscientist. Absorbing the rationale for exploring the nervous system in this way, and learning the required methods and their scientific basis as a beginner with no background in electronics, mathematics, or anything much else that was relevant, led to many low moments. But the work was conceptually and technically fascinating, and I was buoyed by the fact that a lot of obviously smart people thought this was a good way to explore how vastly more complex mammalian brains might operate.

As Potter had promised, Nicholls was indeed a good mentor and, after two years of working diligently to understand how sensory and motor neurons in the leech nervous system were related, I had written two papers of modest interest that were published in the *Journal of Physiology*, the journal of record in those days (an output of one detailed paper a year was typical). But despite my appreciation of his teaching, John and I did not get on particularly well. In addition to what we were doing on a daily basis, I wanted to discuss the broader issues that had always interested me about brains and their function, and John didn't have much stomach for that sort of thing. He told me that as a graduate student, he had been terrified of Katz and the prospect of his failing in his eyes; perhaps as a result, he seemed unwilling to think in grander terms that Katz might have thought silly. By mutual consent, John and I agreed that I would spend the third year of my fellowship in Kuffler's lab (I had already told William Sweet I would not be returning to the neurosurgical program), working with Kuffler's senior collaborator at the time, Jack McMahan. Jack and I had already been looking at the anatomy of leech neurons revealed by the injection of a fluorescent dye that had been developed as a sort of sideline by Ed Kravitz. Jack, a terrific neuroanatomist, was about my age but years ahead of me as a neuroscientist and about to be named to the faculty. We got along famously and had a wonderful time that year, during which he taught me how to do electron microscopy.

During that year, Bernard Katz visited Kuffler's lab, as he regularly did. The friendship and mutual respect between the two first formed in Australia had resulted in a small but steady flow of young neuroscientists between Boston and London, and it was clear that working in Katz's orbit would be a fine next step for me. Although I had learned a lot of neuroscience in my three years as a fellow, I had started from scratch. It seemed foolhardy not to seek more training before going off on my own. The need was all the more obvious because I had decided that working on invertebrate nervous systems was not what I wanted to pursue. And so I asked John and Steve if they would support my case to Katz, which they did. Harvard offered a generous traveling fellowship that would support two years of study abroad, and in the summer of 1971, Shannon and I set off for London with our one-year-old daughter. What I would pursue in Katz's small Department of Biophysics at University College had not been specified, but I was by then sure that I had found my professional niche.

Postdoc at University College

Although Bernard Katz's impact on the course of neuroscience was as at least as great as Kuffler's, the styles of the two men were entirely different. Whereas Kuffler's modus operandi was quintessentially eclectic—he would work on a project with a collaborator or two for three years and then move on to an entirely different problem—Katz was a scientific bulldog. He had seized on the fundamental problem of chemical synaptic transmission in the late 1940s and never let it go. And whereas Kuffler was, superficially at least, an extroverted democrat, Katz was reserved and to some degree an autocrat.

As a result of these personal contrasts, as well as the cultural distinctions between the way science was practiced then in the United States and the United Kingdom, Katz's Department of Biophysics at University College London (UCL) was about as different from the Department of Neurobiology at Harvard as one could imagine. The labs were on the upper floors of one of the old UCL buildings on Gower Street that ran the length of a long London block and housed most of the basic science departments. The rooms of the five faculty members in the department were comfortable but modest, and the surfeit of furnishings, equipment, and supplies that I had been used to in Boston was nowhere in evidence. Even Katz's lab was outfitted with equipment that would have been consigned to storage at Harvard, and his small office contained the same simple furniture that must have been used by A. V. Hill when he was director in the 1930s. Among other things, all this made clear to me that superb science could be done in modest circumstances.

The students and fellows in Katz's domain (about a half dozen of us) were in labs along a short corridor on the floor that included Katz's lab at one end, as well as the supply room and a machine shop. For most of the 1960s, Katz had collaborated with Ricardo Miledi, an extraordinarily talented experimentalist who was Katz's executive lieutenant and the most prominent of the other faculty members. Miledi had a smaller lab adjacent to Katz's where he pursued his own projects with a couple of fellows in addition to his ongoing work with Katz. The other faculty members were on the floor above and included Paul Fatt, a brilliant but eccentric physiologist who had collaborated with Katz in the early 1950s in discovering the "quantal" nature of chemical synaptic transmission; Sally Page, an electron microscopist; and Rolf Niedergerke, another very good biophysicist and a disciple of Andrew Huxley who was working on the properties of heart muscle.

Although I expected to work on a project that would explicitly tap into the expertise and interests of Katz, Miledi, and the others in this new environment, I had no idea when I arrived of what the options in London might actually be. The year I had just spent working with Jack McMahan in Kuffler's lab had been very valuable technically. But my work with Jack had not presented a problem that seemed worth pursuing. Having already soured on the nervous systems of simple invertebrates like the leech, the question for me when I matriculated in Katz's department was what general direction would make sense in that environment and provide me with a starting point for my own research in the academic job I would have to secure when my two-year fellowship ended.

The first day I came to work after getting settled in our flat in Hampstead, Katz invited me into his office to discuss what I might do. Katz, then 60, was austere but certainly not the terrifying figure John Nicholls had described. He listened patiently to my ill-formed ideas and suggested that I should take my time in deciding on a particular project. He mentioned that another postdoc, Bert Sakmann, happened to be at loose ends and was also thinking about what to do next. Accordingly, I met Bert later that day and we chatted about the possibility of working together.

Bert had been medically trained in Tübingen and later in Munich, where he claimed he had gone in pursuit of the fellow medical student he eventually married. In the course of his medical education in Munich, Bert had spent three years carrying out research on the visual system with Otto Kreutzfeldt. Like many of us brought up scientifically in that era, Bert thought that working directly on the visual system or some other part of the brain was a rather daunting prospect and, with Kreutzfeldt's help, had sought out further training with Katz to pursue a future working at the seemingly more tractable level of neurons and their synaptic interactions. We hit it off well because of our similar backgrounds, shared fascination with all aspects of neuroscience, and corresponding opinions about the odd cast of characters and their relationships in the Department of Biophysics. Although Bert was four years younger, we were both recently married, ambitious, and faced the need to land academic jobs when we finished our fellowships. Thus, we wanted to do something significant that would get our careers off and running. Our initial conversation made clear, however, that neither one of us had a very good idea about what that might be.

The issue that finally captured our attention, as well as that of many other neuroscientists at the time, was how neural activity affects synaptic interactions and neuronal connectivity. It had long been apparent that understanding how experience is encoded in the nervous system was a major challenge in neuroscience. Successfully addressing this issue would explain the way we and other animals learn, and unlike the mechanisms of neural signaling, this problem was far from being solved. Because the currency of experience in neural terms is the action potential, it had been assumed for decades that learning involves activity-dependent changes at synapses.

Pursuing some aspect of how activity changes neural circuits thus seemed to us a worthy goal.

This general line of thinking had already motivated a lot of related work in other labs in the 1960s, and one of these was the lab of Per Andersen in Oslo. Andersen, like Kuffler and Katz, was a trainee of John Eccles, albeit many years later. A student of Andersen's, Terje Lømo, had discovered a particularly long-lasting form of potentiation in the brains of rabbits in 1966, a topic he pursued with Tim Bliss, another fellow who had arrived in Andersens's lab in Oslo in 1968. The phenomenon of long-term potentiation that Lømo and Bliss described in the hippocampus was rightly taken to be especially important. Lømo was a fellow in Katz's department at the time Bert and I were considering what we might do, but he was about to leave to work further with Tim Bliss at Mill Hill in north London, where they pursued hippocampal potentiation and firmly established its importance. At University College, however, Lømo had worked on a different project with Jean Rosenthal, another fellow who had just left. Together they had shown that prolonged stimulation of a muscle changed the sensitivity of muscle fibers to the neurotransmitter acetylcholine. This effect suggested another way of exploring how activity could change the behavior of excitable cells. After some further discussion, Bert and I decided that following up on what Lømo and Rosenthal had done would be a fine way to better understand how activity could alter the properties of nerve and muscle cells and, in principle, store information derived from experience.

Our idea about a way to attack this issue was based on an odd fact that neurologists had known and used as a diagnostic tool for decades. When muscle fibers are denervated, they begin generating action potentials on their own (fibrillation). The origin and consequences of this spontaneous activity raised ways to examine the activity-dependent control of postsynaptic cell properties in muscles taken out of an animal and kept alive for a week or so in a Petri dish. In these circumstances, the spontaneous activity in individual muscle fibers could be monitored directly with a recording electrode, the levels of activity experimentally altered by electrical stimulation or a drug and the sensitivity of the fibers to neurotransmitter tested. Katz and Miledi agreed that this seemed to be a sensible project, and so for the next two years, we happily set about exploring these issues. Because neither we nor anyone else in the department knew how to go about this, we fiddled with various chambers, muscles, methods of stimulation, recording electrodes, and culture conditions until we got things to work. Eventually we could record for several days from single muscle fibers and watch their activity wax and wane as spontaneous action potentials or their absence in the fibrillating fibers altered their membrane properties and consequently their sensitivity to acetylcholine. We also stimulated the muscle artificially, showing that denervated fibers kept active never started to fibrillate, and they could be made to stop fibrillating if the spontaneous activity had been allowed to start. Although the results were in the end a modest contribution (another couple of good but rarely cited papers in the *Journal of Physiology*), Bert and I had a fine time being on our own and doing what we thought was interesting.

Katz gave the two manuscripts that Bert and I wrote up at the end of our time in the department his seal of approval and suggested we also show the papers to Andrew Huxley, who was in the Department of Physiology a few corridors away in the warren of UCL buildings. Huxley had been studying muscle contraction since the 1950s in work that was as impressive in its own way as what he had done with Alan Hodgkin on the action potential in the 1940s. Since our work concerned muscle fibers, Katz thought Huxley would be interested and might have useful criticisms. Huxley thought the papers more or less fine, but chastised us for having blacked out some noise around the oscilloscope traces with a marking pen, an innocuous bit of pre-Photoshop improvement of our figures that, for a purist like Huxley, was a cardinal sin.

Bert left London in 1973 to take up an assistant professorship in Goettingen, where within the year, he began a collaboration with Erwin Neher that eventually led to a Nobel Prize in Physiology or Medicine in 1991 for having developed patch clamping, a further step in understanding the basis of neural signaling that Hodkgin, Huxley, Katz, and Kuffler had done so much to advance in the preceding 30 years.

I also had to worry about getting a permanent job and what I would do when I did. While still at Harvard in 1970, I had met Carlton Hunt when, like Katz, he had come by to visit Kuffler. Cuy, who was then in his early fifties, had been Kuffler's first fellow at Johns Hopkins and had spent four years collaborating with him. Together they had worked on stretch receptors in muscle fibers, a project typical of Kuffler's nose for important problems. When I first ran into Cuy at Harvard, he had recently moved to Washington University from Yale and was in the process of building a Department of Physiology and Biophysics in St. Louis, having already put together excellent departments at the University of Utah and then at Yale (where as chair of physiology he had hired John Nicholls). Cuy was then—as always—a distinguished figure, and it was obvious that Steve and the rest of the faculty at Harvard liked him and admired the two departments he had already created. Whatever conversation we had then about future plans must have been quite tentative. I nonetheless took note that—if history and first impressions were any guide—Cuy would be an excellent person to work for.

I met Cuy again two years later in the summer of 1972 when he visited Katz at University College. Cuy had done a sabbatical year in Katz's lab a decade earlier when he had taken a break from muscle spindles to study the effects on neurons of cutting their axons, thus interrupting the connection between the nerve cells and their targets. He was a great admirer of

Katz, and took pains to visit whenever he was in England. Cuy took me to lunch to discuss what I had been doing and the possibility of joining his new department. We agreed over coffee that I would visit St. Louis later that fall to have a look. Although the trip in late October of 1972 included the few other places that had indicated some interest in hiring me, I liked St. Louis, Washington University, and the potential colleagues I met there. Washington University had a rich history of research in neuroscience, but most important, I felt I would be comfortable working in a department run by Cuy and that he would provide guidance to someone still relatively untutored in science and the ways of academia.

And so, with some difficulty, I convinced Shannon that St. Louis was the right place for us—or for me, she would no doubt wish to add—and we arrived in the Midwest on a sweltering day toward the end of the following summer.

Washington University

Given the need to teach the full range of physiology to the medical students, the Department of Physiology and Biophysics Cuy had put together included people who worked on the lung, kidney, and heart. Nonetheless, Cuy's enthusiasms clearly favored neuroscience, and 6 or 7 of the approximately 15 faculty members were neuroscientists. In addition to me, the faculty included Carl Rovainen, who had been a graduate student with Ed Kravitz at Harvard and worked on the nervous system of the lamprey; Mordy Blaustein, who had been a postdoctoral fellow with Hodgkin at Cambridge and worked on the role of calcium ions in cell signaling; and Alan Pearlman and Nigel Daw, both of whom had been fellows in Hubel and Wiesel's lab at Harvard and were continuing to work on the visual system.

Although my initial interests in neuroscience had been anything but reductionist, everything I had done over the preceding five years had been at a simple model systems level. Thus, I was ill prepared to launch into a project that focused on the structure and function of the brain. But I was at least determined to work on nerve cells in a mammal as a step in the right direction, and on problems that would have more pertinence to brain function and organization than the projects I had cut my teeth on.

While still in London, I had of course given some thought to the possibilities. With Jack McMahan, I had worked on autonomic ganglia, a staple of the work that was then going on in Kuffler's lab. Studying these accessible collections of neurons and their connections with both the central nervous system and peripheral targets seemed a good compromise between plodding onward with some aspect of a model synapse like the neuromuscular junction and a more direct attack on some aspect of the brain, which I knew very little about. Autonomic ganglia had been the focus of many key studies of the nervous system since the middle of the 19th century and had set the stage for understanding neurotransmitter action at synapses and, ultimately, for Katz's discoveries of the detailed mechanism of chemical synaptic transmission.

Whatever the merits of choosing the autonomic system, getting started in St. Louis depended on much more than simply picking a reasonable topic to pursue. In this, Cuy was a great help, and I soon understood why he had attracted such good people to the three different departments that he had organized by then, and why their research generally flourished. He was every bit the paternal adviser I had imagined and helped me to get going in all kinds of ways, many of them having nothing to do with science. After I had been plugging away for a couple of months with the equipment that he had arranged to have waiting for me in St. Louis (new and much finer than what I had been used to during the preceding two years at UCL), he came by the lab one day to ask why I had chosen not to enroll in TIAA-CREF, the academic pension fund. I told him that I really wasn't worried about retirement at that point and that Shannon and I couldn't afford to pay the monthly contribution. He patiently explained what an annuity was, the virtues of compound interest, and why this eventually would be important, as of course it was. More to the point, he raised my salary that very day so we could afford to make the contribution.

Working on neuronal connections in the mammalian autonomic system was, as it turned out, another good choice. Although I saw this work as a stepping stone toward a more direct attack on problems explicitly related to brain function, the step eventually consumed about a dozen years with results that, in contrast to what I had done up to that point, were regarded as important. During the first few years in St. Louis, I undertook two projects in the peripheral autonomic system of mammals. The first was directly inspired by observations John Langley had made 80 years earlier. In the course of neural development in embryonic and early postnatal life, connections between nerve cells must be made appropriately. Experience later in life is, of course, important in the ultimate organization and further refinement of connections, but the idea that the human or any other brain comes into the world as a *tabula rasa* is silly. Nervous systems at birth are already connected in detailed and highly specific ways based on the experience of the species over evolutionary time. The mechanisms that produce this specificity of connections during development were unclear in 1973 and to a surprising degree still are.

Langley had examined this issue at the end of the 19th century, making use of the fact that neurons at different levels of the spinal cord innervate neurons in sympathetic ganglia in a stereotyped way. In the superior cervical ganglion, for example, cells from the highest thoracic level of the spinal cord (T1) innervate ganglion cells that project in turn to smooth muscle targets, such as the muscle that dilates the pupil, whereas neurons from a somewhat lower level of the cord (T4) innervate ganglion cells that cause effects in other targets, such as constricting the blood vessels of the ear. Langley had assessed these differences in the innervation of the ganglion simply by looking at these peripheral effects while electrically stimulating the outflow to the ganglion from different spinal levels in anesthetized cats, dogs, and rabbits. When he stimulated the outflow from the upper segments of the thoracic spinal cord, the animals' pupil dilated on the stimulated side without any effect on the blood vessels of the ear, whereas when he stimulated the lower thoracic cord segments, the pupil was not affected but the blood vessels in the ear on that side constricted. Moreover, when he cut the sympathetic trunk that carried the axons to the ganglion and waited some weeks for them to grow back, he observed the same pattern of peripheral responses. Langley thus surmised that the mechanisms underlying the differential innervation of the ganglion cells must occur at the level of synapse formation on the neurons in the ganglion. He further suggested that selective synapse formation is based on differential affinities of the pre- and postsynaptic elements arising from some sort of biochemical markers on their respective surfaces.

Given these studies and more modern ones by Roger Sperry at Caltech, it seemed well worthwhile to pursue the issue of neural specificity at the level of electrical recordings from individual neurons in autonomic ganglia. Arild Njå, a postdoctoral fellow from Oslo, who was the first to come my way, and I pursued the merits of this idea in the autonomic system of guinea pigs by dissecting out the whole upper portion of the sympathetic chain, keeping it alive in a chamber, and making intracellular recordings from individual neurons in the superior cervical ganglion while stimulating each of the input levels from the spinal cord. The results showed that the synaptic connections made on ganglion cells by preganglionic neurons of a particular spinal level are indeed preferred, but that contacts from neurons at other levels are not excluded. Furthermore, if the innervation to the superior cervical ganglion was surgically interrupted, recordings made some weeks later indicated that the new connections again established a pattern of segmental preferences. Thus, neurons of the spinal cord associate with target neurons in the autonomic ganglia of mammals according to a continuously variable system of preferences during synapse formation that guide the pattern of innervation during development or reinnervation without limiting it in any absolute way.

Although this work with Arild resulted in several good papers, it was another project I had begun in parallel that eventually occupied most of my attention over the next decade. The ideas on which this work was based came from another direction altogether. The theme that Bert and I had been working on in London was control of the signaling properties of neurons (although we used muscle cells as a model), and I continued to think—along with many others—that such modulation of signaling and its effects on connectivity over the long haul was especially important. In the first couple of papers to come out of my lab in St. Louis, I showed by electrophysiological recording that the efficacy of the synapses made by the spinal neurons on the neurons in the superior cervical ganglion declined over the first few days after the axons from the neurons to peripheral targets in the head and neck had been cut, and that this decline occurred in parallel with the loss of a majority of the synapses made on the ganglion cells that could be counted in the electron microscope. Because the loss of synapses from the neurons was reversed when the axons grew back to their peripheral targets, the conclusion seemed clear: the synaptic endings made on nerve cells do not just sit there but have to be actively maintained. And whatever the mechanism, this maintenance depended on the normal connections between nerve cells and the targets that they innervated. The clarity of these results in a relatively simple system of mammalian neurons was news, and it encouraged further studies along these lines.

This research led to the beginning of a long collaboration with Jeff Lichtman and a deepening friendship with Viktor Hamburger, both critical determinants of how this work progressed. Jeff appeared in my lab one day in 1974 and asked if he could chat about his future. He was then a second-year med student and knew me from the lectures on neural signaling I had given to his class some months before. Jeff was in the MD/PhD program, and he was trying to figure out what to do for his doctoral work. He seemed nervous and lacked a good reason for wanting to work with me or ideas about what to do. I think he simply saw me as someone who was young and ambitious and who, based on the lectures he had heard, might be a good mentor. My inclination was not to take him on since my experience at Harvard and UCL had been that the best people populated their labs with postdoctoral fellows rather than graduate students. But before reaching a decision, I thought it would be a good idea to ask Cuy. He pointed out that the MD/PhD students were a highly select group, that Jeff would not cost me anything since the program was fully funded by the National Institutes of Health, and that unless I had a very good reason not to I should certainly take him on. Cuy was indeed right: Jeff was—and remains—one of the smartest and most imaginative people I have known in neuroscience and went on to become a major figure in his own right.

Getting to know Viktor Hamburger was equally important. Hamburger was far and away the most notable neuroscientist at Washington University in 1973. Because he was in the Biology Department on the undergraduate campus, I had not met him on my trip to St. Louis as a faculty candidate, and to my great embarrassment, I knew little or nothing about him or his work when I arrived in St. Louis. This woeful ignorance brought home to me the parochial nature of my training up to that point. Viktor was a consummate biologist and my conversations with him about his work and neural development led me to think more and more about what nervous systems do for animals and less about the details of neurons.

As I gained some familiarity with Hamburger's work, it dawned on me that his expertise was especially relevant to what I was doing in the autonomic system, or at least to the part that involved looking at the failure of synaptic maintenance when neurons were cut off from their peripheral targets. Viktor had used the embryonic transplantation techniques learned from Hans Spemann to either add or take away limb buds in embryonic chicks, assessing what happened to the spinal neurons that would have innervated the ablated limbs, or that innervated the extra peripheral targets. The upshot of this work begun in the 1930s was to establish the phenomenon of target-dependent neuronal death or survival. By the 1970s, neuronal death regulated in this way during development had been shown to be a general phenomenon in the peripheral nervous system and in some parts of the central nervous system. A corollary was that the developing neurons in the spinal cord were competing for acquisition of the postulated agent, dying off if they didn't get enough of this "trophic" stuff. This work on the regulation of neuronal numbers in early development by trophic interactions had been greatly advanced by a collaboration that Hamburger began with Rita Levi-Montalcini in the late 1940s. Their work together lasted for about eight years and led to the discovery of nerve growth factor, a trophic molecule derived from smooth muscle that is the "nourishing" agent for at least two types of neurons, one of which was the nerve cell type in the ganglia of the sympathetic nervous system I had been working on. Nerve growth factor has served as a paradigm for the interactions between nerve cells and their targets ever since and remains the best example of trophic interactions in neurobiology.

What I learned from Viktor in the 1970s about neural development and nerve growth factor had a significant impact on what was going on in my lab, where by now several people were toiling away on the formation and maintenance of synaptic connections in the simple and accessible systems that various autonomic ganglia in mammals provided. Like Hamburger, I had never had much interest in studies at the molecular level; among other reasons, my brief but dismal experience with neuropharmacology research as a med student left a lingering bad taste and most molecular studies seemed to me then (and still do) to be learning more and more about less and less. The nerve growth factor, however, was an exception. This agent not only promoted the survival of the very neurons we were studying but also influenced the growth of the axonal and dendritic processes of the classes of neurons that were sensitive to it, and by implication the synaptic contacts they made. It was not hard to imagine that competition for and acquisition of such factors was the basis of the maintenance of synaptic connections we had been providing evidence for and that this "trophic theory" of how synapses were regulated in the nervous system could well be a general rule.

The idea was that each class of cells in a neural pathway was supporting and regulating the connections it received by trophic interactions with the cells it innervated down the line, resulting in a coordinated chain of connectivity that extended from the periphery centrally to the spinal cord and ultimately on through the controlling centers in the brain. The aim in this work on synaptic connectivity in mammals was not to sort out which molecules might be involved (the paradigm provided by nerve growth factor was sufficient evidence on that score and by the mid-1970s many labs were studying this agent), but rather the governing principles of neuronal competition. In pursuing that goal, Jeff Lichtman was the prime mover. The main problems that concerned us for the next several years were the nature of competition among the axons that innervate target nerve cells and how the signaling activity of competing nerve cells affects the balance of synaptic connectivity. The theme was the conviction that nerve cells and their targets must interact in sorting out the connectivity of functioning circuits in much the same way that elements in an ecosystem eventually establish an equilibrium as they compete for limited resources.

The closest anyone had come to directly exploring the issue of synaptic competition by the mid-1970s was a study of the developing innervation of skeletal muscle fibers carried out by Michael Brown, David Van Essen, and Jan Jansen. I didn't know Brown, but Van Essen had been a graduate student at Harvard when I was there (he joined the Nicholls lab for his doctoral work about the time I left to work with Jack McMahan), and Jansen had worked in the Nicholls lab when on sabbatical from his position in Oslo that same year. Back in Oslo a few years later, they had shown that during the first few weeks of postnatal life, each fiber in a rat muscle is contacted by more nerve terminals from different axons than persist in maturity, providing another clue about the nature of synaptic competition and maintenance. A natural question was whether the innervation of neurons followed the same rules as muscle fibers, and Jeff's thesis showed that it did.

Although understanding the interactions among axon terminals and the synapses they make on target cells remains incomplete, some important principles emerged from the work carried out by Jeff and several other fellows in the lab over the next few years. One is that the spatial configuration of a neuron is a critical determinant of the innervation it receives. For nerve cells without dendritic processes, the end result of the initial competition is innervation by many synaptic endings, all arising from the same nerve cell axon. If a target nerve cell has dendrites, however, the number of innervating axons increases in proportion to the number and complexity of its branches. Moreover, once a given axon makes some synapses on a target neuron, the axon is informed by the conjoint activity of the pre- and postsynaptic neurons that the target cell is a favored site for the elaboration of additional synaptic endings. This focusing of synapses occurs despite the presence of numerous other valid target neurons in the immediate vicinity. Thus, the synaptic terminals made on a target neuron act as sets rather than as individual entities during the establishment of neural circuits. This and much other evidence implies that neural activity—action potentials that release transmitter at the synapses in question—is importantly involved in circuit formation.

Intriguing though these observations were, it was increasingly clear that to understand what was going on during the formation and maintenance of synapses, one would have to figure out a way to directly monitor the progress of synaptic contacts on the same target cell over periods of days, weeks, months, or longer. This goal seemed technically feasible in the peripheral nervous system and would allow us to watch how competition operated during development and how synaptic connections went on being modified in maturity. Since encoding experience during life depends on functional and anatomical changes in neural connectivity, the expectation was that synaptic connections would change gradually over time and that we would be able to witness the process in action. A next step was therefore to figure out how to observe the same synapses chronically.

Our first stab at this goal was based on the ability to identify the same neuron in the autonomic ganglia of a living animal on different occasions. Given that each neuronal cell body has a somewhat different appearance in the cobblestone-like pattern of cells visible on the surface of a ganglion, it is not hard to find the same neuron during an initial surgical exposure and at a second such operation after an arbitrarily long interval. An identified neuron thus could be injected with a non-toxic dye and the configuration of its dendrites photographed. By carrying out the same procedure weeks or months later, we could ask how dendritic branches changed over time. Since the dendrites of ganglion neurons are studded with synapses, any change in the architecture of the dendritic branches would imply ongoing changes in synaptic connectivity. It was evident from these initial studies that dendrites are continuously remodeled, and therefore that the synaptic connectivity of the neurons must be changing as well.

Monitoring the synaptic endings themselves over time would of course be more revealing, and this is what we set out to do next. The problem in this project was that, unlike the cell bodies, synapses are far too small to be directly injected with a dye. To visualize synapses, we needed a dye that the terminals would take up quickly and would then diffuse away without damaging the endings. Finding such a reagent was a matter of trial and error, and the person who undertook this thankless task was Lorenzo Magrassi, a smart, hard-working medical student from Italy who had come to spend a year in the lab in 1985. Lorenzo, who knew quite a lot of chemistry, applied one plausible reagent after another to synaptic endings on mouse muscles in a dish while he observed the results. When after many weeks of this he finally succeeded in finding a dye that met these criteria, Jeff Lichtman (who was by then a faculty member at Wash U), Lorenzo, and I began monitoring synapses on muscle fibers over months by finding and re-staining the same synaptic endings. The method also worked for the synaptic endings on identified ganglion cells, and synapses on neurons could be followed over time in the same way. In both cases, synaptic terminals gradually changed, slowly on mature muscle fibers and faster on neurons.

Although this effort to understand the formation and maintenance of synapses had been successful by the mid-1980s, things as I saw them were not going so well. The reasons were several and had only partly to do with science. With respect to the science, it was not clear at that point what to do next. Directly monitoring synaptic change in muscle fibers and ganglia had been a fine start. But no one was going to get very excited with this work if it could not be extended to synaptic stability in the brain. It was the brain, after all, that determined behavior and the cognitive processes I and everyone else wanted to understand. I had viewed these studies of synapses in ganglia and muscle as simple systems for getting at what was likely to be happening in more interesting parts of the nervous system. But the techniques we had been using were difficult enough to apply in the peripheral nervous system, and for various reasons, were hard to imagine applying to synapses in the brain. Within a decade, further advances in molecular biological methods resolved this impasse by providing labels that could be introduced into neurons by gene transfection. This methodology eventually allowed Jeff and his collaborators and others to begin to tackle these sorts of problems in the brain. But that possibility was not on the horizon in 1985.

Other factors were also at work. Cuy Hunt had retired and moved to France. As a result, I (along with Jeff Lichtman and Josh Sanes) had moved to the Department of Anatomy and Neurobiology in 1986. Gerry Fischbach was running the department as Max Cowan had left to take a position as the chief scientific administrator at the Howard Hughes Medical Institute. Gerry was a fine chair. But he was a peer, creating a situation quite different from the paternal figure Cuy had been. Finally, there was an increasing awkwardness between Jeff Lichtman and me. Jeff by then had his own successful lab and, although we had continued to collaborate, the relationship was no longer the one I had enjoyed for many years. We were now working on similar issues and, to some degree, had become competitors.

In a couple of years I would be 50, and the undeniable fact of middle age combined with these several circumstances triggered another bout of depression, this one more serious than those I had experienced before. Although I kept experimenting, writing papers and books (*Principles of Neural Development*; *Body and Brain*) and carrying out teaching assignments, my usual enthusiasm had begun to wane. I saw a psychiatrist who started me on an antidepressant, and when the drug he prescribed didn't work, my depression deepened. Mainly as a result of my wife's support, the counsel of another psychiatrist, a different medication, and perhaps just the passage of time, I gradually began to see a plausible future again.

Having returned to a better frame of mind, I felt I had achieved enough success to take some bigger scientific chances. I had started out with broad philosophical interests in the brain, but by virtue of my training, the people and the science that I admired, and the overall direction of neuroscience, I was still de facto a reductionist. With perhaps another 20 or 25 years or so to go, I felt I owed it to myself to at least think about doing something that might go beyond the conventional framework that I had assiduously learned, worked within, and taught for what by then was two decades.

Tackling the Brain

If I was going to pursue research on some aspect of the brain, it was clear I would need a remediation and the first order of business was to find a good teacher. In this regard, I was especially lucky in 1987 when Anthony LaMantia, who had just finished his doctorate with Pasko Rakic at Yale, got in touch with me about joining the lab as a postdoctoral fellow. Rakic was the most accomplished and imaginative neuroanatomist in the country, and I had followed his work on the development of the primate brain closely. His knowledge and talent rubbed off on his trainees, and given my new inclination, Anthony's arrival in the lab the following year was a godsend. I learned far more from him over the next few years than he from me.

Relearning brain anatomy, however, was only preliminary to figuring out a good problem to explore. Typically, investigators extend their research in directions with which they are familiar, making an educated guess about what an interesting tangent might be. This is what Anthony and I did, ultimately deciding to tackle neuronal development and stability in the olfactory system. By 1988, the work on monitoring synapses over time in the peripheral nervous system was winding down for me. Anthony and I would like to have monitored synapses in some region of the living brain, but there seemed no way to do that. We therefore settled on what we thought was the next best thing: monitoring the development and maintenance of brain "modules."

The modular units we chose to look at first were the glomeruli in the olfactory bulb of the mouse. The reason for the choice was not that these were the most interesting cortical patterns—that prize went to ocular dominance columns in the visual cortex. Glomeruli, however, were practical modules to begin with. Mice were cheap and we would have to use lots of animals to work out methods for exposing the brain, staining these units with a nontoxic dye, and repeating the procedure to examine the same region weeks later. We succeeded over the next year or so showing that new units were added among the preexisting ones as the mouse brain developed. These findings about the olfactory system were not, however, news that anyone had been waiting for. The focus of interest cortical modularity and the visual system and it was the brain region that had stimulated the most ardent debates about the role of modularity.

As a student in Rakic's lab, Anthony had had plenty of experience working with rhesus monkeys, and so we turned next to the monkey visual cortex. For a variety of reasons, it was impractical to carry out repeated monitoring in the same monkey as we had done in the mouse. We again settled for the next best thing. Given what we had found in the mouse olfactory bulb, it seemed reasonable to look at the overall number of modular units in the visual cortex shortly after birth and in maturity in different monkeys. If the numbers were significantly different, it would follow that units had been added as monkeys matured, much as we had documented in the olfactory brain of the same mouse. The easiest units to look at in the monkey visual cortex were the so-called "blobs." These visual system modules had not attracted the same attention as ocular dominance columns, but they were discrete and could be easily counted.

The project, however, was problematic from the outset. Although I had worked on lots of different species over the years, including small monkeys, adult rhesus monkeys are large and often nasty. The expense, the character of the animals, and the knowledge that the project would be only a stepping stone to a more direct approach made us hurry along and eventually publish a wrong conclusion. On the basis of the first few animals in which we counted blobs at birth and in maturity, it seemed reasonably clear that these units were being added. Anxious to stake this claim in the monkey visual system and convinced that the results we had seen in the mouse olfactory bulb indicated a general rule, we went ahead and published a short paper to that effect. When we completed the study with a larger complement of monkeys, however, we found no significant difference in the initial and mature number of blobs in the visual cortex. We corrected our mistake in the full report of the project and no one seemed to have paid much attention to our error, but I realized that I had pushed too hard in the interests of being recognized as a player in the community of "brain scientists." This minor fiasco left me considerably less confident about making the transition from the peripheral nervous system to the brain. It also left me with the need to come up with another research direction, as there seemed no great merit in pursuing the long-term stability of modular units in the visual cortex (to judge from our work on blobs and other evidence we should have paid more attention to, they are pretty stable over primate development).

Duke

While all this was going on, our lives were changing in another way. In 1990, I accepted an offer from Duke University to start a Department of Neurobiology, and Shannon and I and our younger daughter had moved to North Carolina (which is where Anthony and I carried out the work on monkey blobs). Duke had raised the sum required to hire and set up about a dozen new faculty and had put up a new building to house the department.

This largesse coupled with the quality of the university and its ambitions presented an opportunity that was hard to turn down, even though it promised some administrative work that I had always shunned.

The move turned out to be significant in many ways, almost all of them positive. My less than robust mental state when I accepted the job at Duke benefited greatly from the change of scene and the challenge of starting a new department. I had been at Washington University 17 years, and my crankiness at the end of that time, the problematic relationship with Jeff Lichtman, and my desire for a new scientific start were all more or less resolved in one fell swoop. The move was also a big plus for Shannon. Shannon (known as Shannon Ravenel in the publishing world) had been a successful young fiction editor with Houghton Mifflin in Boston when we married in 1968, but had given up her job when we moved to London in 1971. During our first few years in St. Louis, she had taken on a series of minor editorial jobs to make ends meet that were as demeaning to her as it would have been for me to teach high school health science at that point in my career. Her professional situation improved in 1977 when Houghton Mifflin asked her to become the series editor of their annual anthology "Best American Short Stories," a job she could do in St. Louis that entailed selecting stories published each year in North American periodicals. Shannon's situation improved again in 1982 when her friend and mentor, Louis Rubin, asked her if she would be interested in starting a literary publishing company in Chapel Hill, where he was professor of English at the University of North Carolina. She agreed, and had been exercising her role in this new venture from St. Louis. But as Algonquin Books of Chapel Hill grew increasingly successful, this arrangement had become awkward. As Duke is only 10 miles from Chapel Hill our move solved problems for both of us (Algonquin Books was bought by Workman Publishing Co. in New York in 1989, and continues to flourish).

The first of several new postdoctoral fellows to join my lab at Duke was David Riddle, a PhD from the University of Michigan, and the direction that seemed most attractive involved yet another region of the mouse brain that had long been of interest: the somatic sensory system. Although not as thoroughly plowed as the visual system (and for many people, intrinsically less interesting), the somatic sensory system had some advantages. The major attraction was that the cortical representation of the body surface can be seen and measured.

David and I (and eventually another fellow, Gabriel Gutierrez) wanted to see whether the regions of sensory cortex that experienced more neural activity during maturation captured more cortical area than less active brain regions. We could explore this question by measuring the area occupied by different components of the somatic sensory map at different ages, asking whether the more active areas grew faster. If this correlation could be established, the implication would be that the neural activity generated by an animal's experience in life was being translated into the allocation of more cortical area to process the relevant information (i.e., a manifestation of the influence of neural activity on cortical connectivity). This turned out to be the case: the more active cortical regions expanded relatively more during maturation than less active ones.

Taking stock, by the early 1990s, I had put in about five years working on these various projects in the brain at Duke and felt more or less knowledgeable about the issues with a reasonable grasp of brain anatomy. To show my willingness to participate in the grunt work of the new department, I was teaching Duke med students each spring; although I was certainly no expert, I no longer embarrassed myself when answering questions about neuroanatomy. Although work on the growth and organization of the cortex as a function of activity continued, as much from scientific boredom as from any clear goal, I began thinking about vision more broadly, fiddling around with some small projects on perception that seemed interesting but minor asides to the mainstream neuroscience that was plodding along in the lab.

Visual Perception

Perception—that is, what we see, hear, feel, smell or taste—is generally thought of as the end-product of sensory processing, eventually leading to appropriate motor or other behavior. But if one thinks about it, perception is far more complicated than this garden-variety interpretation. Why is it that what we see or otherwise experience through the senses fails to tally with corresponding physical measurements? And what do these discrepancies have to do with the longstanding philosophical inquiry into the question how can we know the world through our senses in the first place? Once I had begun to work on sensory systems, these and other questions about perception kept intruding and were harder and harder to ignore. They are, after all, pretty basic.

Like most mainstream neuroscientists, however, I was leery of devoting much time to questions that generally are looked down on as belonging to psychology or, worse yet, philosophy. I had first gotten a sense of this bias as a postdoc in the Nicholls lab circa 1970, when we had lunch everyday with the Hubel and Wiesel lab. Because they were working on vision, Hubel and Wiesel were familiar with many of the controversies and issues in visual perception. But the only psychologists I remember them taking seriously were people like Leo Hurvich and Dorothea Jameson who devoted their careers to painstaking psychophysical documentation of lightness and color percepts and models of how these phenomena might be explained. When less rigorous psychologists came up in conversation, Hubel would refer to them as "chuckleheads," a term he used quite a lot (and did not limit to psychologists). Likewise, the rest of my mentors and colleagues at Harvard, University College London, and later Washington University didn't waste much thought on psychology or its practitioners; by and large, this sort of work was deemed irrelevant to the rapid progress of the reductionist neuroscience that nearly all of us were doing. Psychology as science was considered not up to par, and philosophical questions were simply nonstarters.

In 1994, I undertook the first of several mini-projects on perceptual issues with another postdoc, Len White, that we both regarded simply as interesting diversions from the tedious project we had embarked on. Len was a superbly trained neuroanatomist who had recently gotten his doctorate with Joel Price, one of Max Cowan's original hires at Washington University. We had been looking at the neural basis of right- and left-handedness by laboriously measuring the cortical hand region in the two hemispheres of human brains. Based on the effect of activity on the allocation of brain space in rodents, we thought that human right-handers would very likely have more cortex devoted to that hand in the left hemisphere where the right hand is represented. Thus, Len and I were in the process of measuring this region in hundreds of sections of human brains removed at autopsy.

People are not just right- or left-handed, but are also right- or left-footed, and, interestingly, right- or left-eyed. To leaven the load of measuring the right- and left-hand regions in what ended up being more than 60 human brains, we started thinking about right- and left-eyed-ness. The question about perception we asked was whether people who were either right-eyed or left-eyed when sighting with one eye (e.g., aiming a rifle) expressed this preference routinely when viewing the world with both eyes. To this end, we covered a large panoramic window with black paper into which we had cut about a hundred holes the diameter of a tennis ball. We asked subjects to simply wander around the room and look at the scene outside though one or another of the holes, which they would necessarily have to do using one eye or the other. This setup mimicked the everyday situation in which we look at the objects in a scene that lie beyond occluding frames in the foreground. As subjects looked at the outside world through the holes from a meter or two away, we monitored whether they used the right or left eye to do so, and whether the eye they used agreed with the eyed-ness they showed in a standard monocular sighting task. It did, although as far as I know, no one paid the least attention to the short paper that we published on this. Doing this work, however, and thinking about the issues involved, was a good deal more fun than measuring the hand region in human brains (which, as it turned out, showed no significant difference between the cortical space devoted to the right and left hand in humans). It also raised eyebrows among my colleagues in the Department of Neurobiology. When they walked by and saw the papered-over window with people wandering around looking out through little holes, it was apparent that some weird things were going on in my lab. The young faculty I had begun recruiting to the new department seemed mildly bewildered at the apparent flakiness of what we were doing, which was very far from neurobiology as they understood it.

A different project in perception we undertook at about the same time was just as peculiar but less trivial and accelerated my transition toward a focus on perception as such. Another postdoc, Tim Andrews, had gotten his degree in the United Kingdom working on trophic interactions and had come to Duke expecting to work with me on some related issue. But when he arrived, the attraction of perception caught him up as well, and he became the first postdoc to work primarily on perception. The eyedness project uncovered a lot of interesting literature, including several papers by Charles Sherrington describing little-known experiments on vision that carried out in the early 1900s. In Sherrington's highly influential work on motor reflexes, one of his principal findings was that actions were routed through a "final common pathway." By this, he meant that the output of all the neural processing that goes on in the motor regions of the brain ultimately converges onto the spinal motor neurons that innervate skeletal muscles, which in turn generate motor behavior. It thus was natural for him to ask whether the same principle might apply to perception.

Sherrington recognized that the sensory nervous system provided a good venue in which to address this question, namely, the processing carried out by the neurons in the visual system that are related to one eye or the other. If the information from the two eyes is brought together in a "final common pathway" in the visual brain, then the combined asynchronous left- and right-eye stimulation should be perceived as continuous light at roughly half the normal flicker-fusion frequency. The result Sherrington obtained, however, was that the on-off rate at which a flashing light becomes steady is identical in the two circumstances. On the basis of this observation—which Tim Andrews and I confirmed—Sherrington concluded that the two retinal images must be united "psychically" rather than physiologically, thus lying beyond his ability (or interest) to pursue.

For better or worse, Tim and I and other students and fellows in the lab continued down this path over the next couple of years, carrying out a series of projects on visual perception that examined other odd phenomena, such as the wagon-wheel illusion in continuous light, the rate of disappearance of the images generated by retinal blood vessels, the strange way we perceive a rotating wire-frame cube, and the rivalry between percepts that occurs when one stares long enough at a pattern of vertical and horizontal stripes. All the while, the lab was carrying on conventional projects on handedness, the way cortical organization was affected by the prevalence of differently oriented contours in natural scenes and other unfinished business in mainstream neurobiology. The reality, however, was an ever-greater interest in perception, and less and less devotion to mining issues of brain structure and function with the sorts of electrophysiological and anatomical tools I was familiar with. In the end it led to far more important work than I had done earlier.

The tipping point came in 1996. By then I was in my late 50s, and after seven or eight years puttering around with how activity affects brain organization, I still hadn't stumbled across anything that was deeply exciting. With perhaps 10 or 15 good working years left, I began to think that I should spend all my remaining time working on perception. I had learned enough about the brain and the visual system to have a sense that the attempt to explain perception in terms of a logical hierarchy of neuronal processing in which properties of visual neurons at one stage determine those at the next was wrong in some fundamental way. No percept had been convincingly explained in these terms and a wealth of visual perceptual phenomena remained unclear. In science, when that much time goes by without success, it usually means that a field is on the wrong track.

I was pretty sure that given my age, the raised eyebrows of my colleagues, and my lack of serious credentials in vision science, it would be an uphill fight to support a lab focused explicitly on perception (up to that point, I had been using money from grants for the ongoing conventional work in the lab to support our perceptual forays). I also sensed that I was coming to be seen as something of an oddball and was less-often invited to high-profile meetings or to lecture at other institutions. Conversely, work on perception doesn't cost much to do, and I knew that if I didn't take the plunge at that point, I would not have a second chance. And so I plunged.

Lightness and Color

The observation in 1997 that set me thinking in earnest about a possible answer to the challenge of perception was a picture. I don't remember the subject, but in the course of a noontime seminar, the speaker showed a popular visual illusion. It was not that the information in a scene influenced perception of some particular part of it—Michel Chevreul, Hermann Helmholtz, the Gestalt psychologists and pretty much everyone else had recognized that. What struck me was that an accumulation of this information arising from trial-and-error behavior in response to retinal stimuli provided a way of getting around the problem presented by the inability of biological vision to measure the physical world. Looking at perception in this way also suggested why the standard ideas about what visual neurons were doing had come a cropper, and perhaps a way of understanding what the connectivity of visual neurons was actually accomplishing. I was excited enough about the idea that perceptions might be determined in this way to go back to the lab after the lecture and seek out Mark Williams, a postdoc who was especially skilled in computer graphics (a methodology that was far more challenging then than it is with today's user-friendly software). I sketched a crude scene and tried to explain what I thought might be going on. Although what I said couldn't have made much sense, it was enough to get Mark interested. Within a few weeks, he created a series of computer programs that we used to test the idea that the lightness values people see are determined by linking accumulated experience with patterns of luminance to perceptions (and other behaviors) that would have been helpful in response to the stimulus in question.

Perceptions of lightness seemed a good place to start. Of the basic qualities that define visual perception (lightness, brightness, color, geometric form, distance, depth, and motion) the most important is seeing relative light and dark. Because it would presumably behoove us to see the world as it "really is," a logical expectation is that lightness derives from the luminance of a stimulus: the more light falling on some region of the retina, the lighter that target should appear. But this expectation is not met; indeed, we never see the world as a photometer measures it. A simple example is that two central patches with the same luminance are perceived differently depending on the luminance of the surround (a phenomenon called "simultaneous lightness contrast"). Over the next year, Mark and I and a bright premed student (Alli McCoy) put together enough evidence to write a couple of papers on how subjects perceived the lightness of test patches in scenes with different empirical meanings. The implication was that the different lightness values we see are determined by accumulated experience with luminance patterns in retinal images.

The problem that we took to underlie these effects is that biological visual systems lack the tools needed to measure real-world parameters. If the lightness values we see were simply proportional to luminance, the result would be a useless guide to behavior. If, however, our sense of lightness is generated empirically—that is, by trial-and-error accumulation of information that reflected successful behavior in response to retinal patterns—this problem could be resolved. Our idea was that the frequency of occurrence of image patterns in human experience would have determined the evolution of the relevant visual circuitry. As a result, neural connections that linked the visual stimuli to operationally useful perceptions would gradually wax in the visual brains of the population. Perceptions arising in this way would not correspond to any particular feature of the stimulus but to the perceptions that had generated successful behavior in the past.

Given this conception of vision, the next step was to test its validity in a more serious way. Pursuing this goal over the next few years depended critically on Beau Lotto, a postdoc who arrived in the lab in 1998. Like Tim Andrews, Beau had done his doctorate in developmental neurobiology in the United Kingdom and had come to my lab with the idea of pursuing some developmental issue in vision. But by the time he arrived, my interest in visual perception was fully in the ascendancy. After some initial backing and filling about what to do, Beau threw himself into the work on perception and had all the skills needed to push things along in new and imaginative ways. He grasped the nub of conceptual or technical problems right away and had the intelligence and tenacity to solve them. Furthermore, he was (and is) as much an artist as a scientist, and his ability to make visual tests and demonstrations was invaluable. Because we had no idea how to acquire or analyze data that could serve as a proxy for human visual experience with luminance, we started with the easier task of showing that some of the most perplexing lightness effects (e.g., Mach bands, the Cornsweet edge effect, and the Chubb effect) had plausible empirical explanations.

Although Beau and I were pleased with what we took to be clever empirical explanations of phenomena that had puzzled people for a long time, the general response of vision scientists was that these accounts were "just-so stories" that could not be taken seriously because they were not connected to information about the receptive fields of visual neurons that everyone assumed would eventually explain perception. This was frustrating because if we were right, the relationship between the properties of visual neurons and perception would never be explained in the logical framework that was then in play. If a wholly empirical strategy of vision is the operating principle, then the visual brain was a welter of neuronal connections built historically over evolutionary and individual time according to all the factors that determine successful behavior. Not surprisingly, people whose careers were founded on the supposition of logical computation did not welcome our ideas.

In an empirical conception of vision, making sense of the neurophysiology underlying perception ultimately would depend on understanding the evolutionary history of the human nervous system in terms of behavior. And that goal seemed impossible, at least in the short term. But if we had a proxy for human visual experience with some aspect of the natural world—say, experience with retinal luminance patterns—we could at least test whether accumulated experience predicted some of the lightness perceptions we had been concerned with. Although we began to think more about this possibility, it was not clear how to proceed in 1999. The easier path was to load on more evidence by examining the perceptions elicited by other visual qualities, asking whether further perceptual puzzles could be accounted for in this way. And the quality that seemed best suited to this purpose was color.

Seeing in color is the perceptual quality generated in many visual animals when the light energy in a stimulus is unevenly distributed, and Beau and I felt pretty sure that color perceptions could also be explainable in empirical terms. Thus, we set about exploring whether the way we see color is the result of accumulated trial-and-error experience with spectral relationships.

We first tested this idea by having subjects adjust the perceived color of a target on a neutral background until it matched an identical target on a colored background, thus measuring the perceptual change induced by the color of the surround. The upshot was that we could enhance or diminish color contrast effects by making the characteristics of a scene either more or less consistent with different sources of the light spectra coming from target patches. For example, when identical targets are presented on backgrounds that include a variety of tiles with spectra designed such that the two arrays are likely to be under "red" and "blue" illumination, the apparent color difference between the targets is relatively marked. Conversely, when the contextual information is consistent with the arrays being under the same illumination, the apparent color difference of the physically identical targets decreased. Because the average spectral content in scenes was the same, these effects could not be explained by adaptation or neuronal interactions at the input stages of the visual system. In empirical terms, however, the color perceptions elicited by the same targets in different contexts—i.e., contrast and constancy—made sense.

Although Beau and I were sold by the outcome of these studies, the response from the vision scientists who we thought might be converted was a collective yawn. The papers we wrote invariably were given a hard time by anonymous reviewers; granting agencies were unenthused; and even local colleagues showed only polite curiosity about what we were doing. Visual physiologists were unimpressed because we said nothing about how any of this could be related to the properties of visual neurons. Psychologists were equally unenthusiastic pointing out that we failed to rebut (or often even mention) other explanations. Although there was certainly some truth in this complaint, the main objection seemed to be that in coming at these issues from a different tradition, we lacked the necessary credentials to intrude in this arena and failed to appreciate the conventional wisdom.

Analyzing Spectral Databases

A way to determine the accumulated experience we took to underlie these lightness and color phenomena was to examine spectral relationships in databases of natural scenes. The way to do this was devised by two postdoctoral fellows who recently had come to the lab from China, Fuhui Long and Zhiyong Yang. Fuhui was a quiet young woman whose retiring demeanor concealed a vivid intelligence and a determination I had rarely encountered. Fuhui had received a doctorate in computer science and electrical engineering and had been a postdoc in the Department of Electronic and Information Engineering at Hong Kong Polytechnic University, where she had worked on image processing and computer vision. As a result, she was familiar with a wide range of technical approaches to image analysis; her purpose in coming to my lab was to gain some knowledge about the biological side of things.

Fuhui collected about a thousand high-quality digital photographs of representative natural scenes and wrote the programs needed to extract the physical characteristics associated with hue, saturation, and color brightness at each point in millions of smaller samples taken from these images. Our assumption was that this database would fairly represent the spectral relationships that humans had always experienced and thus allow us to predict the classical colorimetry functions. If the organization of the perceptual color space has been determined this way, then the effects of routinely experienced spectral information should be evident in the ability of subjects to discriminate color differences as the wavelength of a stimulus is varied. The relevant psychophysical functions could then be compared with the functions predicted by analyzing the spectral characteristics of millions of samples from natural scenes. Although certainly not perfect, there was good agreement between the psychophysically determined functions and the functions we predicted from the empirical data.

Just as important was to go back and show that the perception of lightness could be explained by the frequency of occurrence of luminance patterns, and Zhiyong Yang set about this task. He had received a doctorate in computer vision from the Chinese Academy of Sciences, and before coming to the lab, he had done postdoctoral work with David Mumford at Brown working on pattern theory and with Richard Zemel at the University of Arizona working on probabilistic models of vision. Like Fuhui, his skills were well suited to extracting empirical information from scenes to figure out how this information could explain the otherwise puzzling way we see lightness. Much like accounting for colorimetry functions, the idea was that human experience with the patterns of light intensities in achromatic retinal images would account for lights and darks that we actually see. This universal experience would have led to visual circuitry that determined perceived lightness values of the elements in a given pattern according to their relative rank of in all achromatic patterns witnessed over individual and evolutioary time. Using this general approach, Zhiyong showed that the frequency of occurrence of luminance relationships extracted from natural scenes with templates configured in the form of other stimuli predicted a variety of complex lightness percepts.

Geometry

If vision operates empirically, then the same scheme should also explain the way we see spatial intervals, angles, shapes, and distances. It was not clear to anyone in the lab, however, how to pursue this. The answer appeared in the person of Catherine Qing Howe, another superb product of the Chinese educational system. At age 10, Qing had been chosen by the Chinese Academy of Sciences as one of 30 intellectually gifted children to receive an individualized curriculum in the Beijing Middle School system. She entered Peking Union Medical College at age 15, the youngest student they had ever taken. There she became increasingly interested in cognition and behavior and determined to pursue these topics in the context of psychiatry. Her idea (much as mine had been as a first-year medical student with similar intentions) was that the best way to understand these issues was through pharmacology. During her last year in med school she was elected to represent her class in an exchange program with the University of California San

Francisco Medical School. The experience convinced her to emigrate to the United States, and after receiving her medical degree in 1997, she matriculated in the neurobiology graduate program at Duke and, after a false start in molecular biology, ended up in my lab.

Qing recognized that if we were going to explain geometrical percepts in empirical terms, she would have to determine the frequency of occurrence of geometrical images projected onto the retina, much as we had been assessing the frequency of luminance and spectral distributions in images. Accordingly, she used a laser range finder to determine the frequency of the occurrence of retinal images generated by real-world geometry. To understand this approach, consider the perceived length of a line compared with its actual length in the retinal image. In human experience, the length of a line on the retina will have been generated by lines associated with objects that have many different physical lengths, at different distances from the observer and in different orientations. As a result, it would be of no use to perceive the length of the line in the retinal image as such. In a wholly empirical concept of vision, the length seen would be determined by the frequency of occurrence of any particular length in the retinal image relative to all the projected lengths experienced by human observers in the same orientation.

Qing first asked how the perceived length of a line changes as its orientation is varied. As psychologists had repeatedly shown, the same line looks longer when presented vertically than horizontally. Oddly, however, the maximum length is seen when the stimulus line is oriented about 25 degrees from vertical. In the empirical framework, the apparent length elicited by a line of any given projected length on the retina should be predicted by the rank of the line on an empirical scale determined by its frequency of occurrence. Qing tested this explanation by assessing the projections generated by the laser-scanned scenes. By extracting all the projected straight lines from the database that corresponded to geometrical straight lines on surfaces in the three-dimensional (3-D) world, she compiled the frequency of occurrence of projected lines at different orientations. In effect, this analysis represents human experience with lines of different lengths and orientations in retinal images. When Qing used the laser-scanned data to predict how the same line at different orientations should be seen on the basis of their empirical rank, the predicted percepts matched the function that describes the lengths people actually see.

Qing and Shuro Nundy (another student involved in much of this work) took on another challenge: rationalizing the perception of angles. Like the apparent length of lines, an intuitive expectation about the perception of angles is that this basic feature of geometry should scale directly with the size of the angle measured with a protractor. This is not, however, what people see. It has long been known that observers tend to overestimate the magnitude of acute angles and underestimate obtuse ones by a few degrees.

The frequency of occurrence of angle projections generated by the geometry of the world also could be determined from laser range images. The supposition was that this information would determine the odd way we see angles, which it did.

Motion

The last of the basic visual qualities we explored was how the brain perceives motion. One of the things that puzzled scientists thinking about motion is the obvious way that motion perception is affected by context. Depending on the circumstances, the same speed and direction projected on the retina can elicit very different percepts. Although such phenomena were often treated as special cases or simply ignored, if what we had been saying about vision was true, then the perception of motion should have the same empirical explanation as perceptions of lightness, color, and form. For obvious reasons, observers must respond correctly to the real-world speeds and directions of objects, and these responses are certainly initiated by the speeds and directions of objects that determine stimulus sequences projected onto the retina. But when objects in 3-D space project onto a two-dimensional (2-D) surface, speed and direction are conflated in the resulting images. As a result, the sequence of positions in 3-D space that define motion in physical terms is always ambiguous in the sequence of retinal positions generated by moving objects. If contending with this problem depended on the empirical framework that we had used to rationalize other visual qualities, then the perceptions of motion elicited by image sequences should be predicted by the frequency of occurrence of the retinal image sequences humans had experienced.

Testing this idea, however, was not so easy. There was no technical way to collect the information that we needed about the direction, speed, and 3-D position of moving objects. We could, however, approximate human experience with object motion in a virtual world in which moving objects were projected onto an image plane (a stand-in for the retina). This simulated approximation of motion experience could then be used to predict the perceived speeds and directions seen in response to motion stimuli, thereby testing the idea that motion perception is also generated empirically.

Specific examples people had struggled to explain are the flash-lag effect, which concerns the perception of speed, and aperture effects, which concern the perception of direction. The challenge of explaining these effects in empirical terms was taken up by two postdocs, Kyongje Sung and Bill Wojtach. Kyongje had gotten his doctorate at Purdue studying how people carry out visual search tasks and was the first card-carrying psychophysicist to join the lab. Bill had gotten his doctorate in philosophy at Duke working on perception; he had come to lab meetings while working on his doctorate and eventually decided to pursue a career that tapped into both philosophy and neuroscience. Bill and Kyongje made a somewhat unlikely scientific pair, but they complemented each other's skills and eventually showed that perceptions of motion are based on the same strategy as other visual qualities.

They first explored the flash-lag effect, a phenomenon that had been kicked around for decades without agreement about its cause. When a moving stimulus is presented in physical alignment with an instantaneous flash that marks a point in time and space, the flash is seen as lagging behind the moving stimulus. Moreover, the faster the speed of the stimulus, the greater the lag. In the framework we had been pursuing, the flash-lag effect should be a consequence of the same empirical strategy applied to the perception of object speed. To test this supposition, Bill and Kyongje asked whether the amount of lag seen by subjects over a range of speeds is accurately predicted by the relative frequency of occurrence of image sequences arising from 3-D object motion transformed by projection onto the retina. Their first step was to vary the speed of the moving object over the range that elicits a measurable flash-lag effect. They then sampled the image sequences generated by tallying up the frequency of occurrence of the different projected speeds generated by the millions of possible sources moving through the simulated 3-D environment. If the flash-lag effect was indeed a signature of visual motion processing on an empirical basis, then the lag reported by observers for different stimulus speeds should be accurately predicted by the relative positions of different image speeds arising from the influence of this accumulated experience. And it was.

They next explored the perception of direction by studying the changes that occur when moving objects are seen through an occluding frame (an "aperture"). For example, when a rod oriented at 45 degrees moving physically from left to right at a constant speed is viewed through a circular opening that obscures its ends, its perceived direction of movement instantly changes from horizontal to downward at about 45 degrees from the horizontal axis. The simplest phenomenon to explore was the altered direction of motion induced by a circular aperture. The frequency of occurrence of lines that can move across a circular aperture with both ends occluded is strongly biased in favor of the direction orthogonal to the line. Bill and Kyonje showed that this is the direction humans have experienced most often whenever moving lines are seen through a circular aperture.

These empirical explanations of flash-lag and aperture effects again indicate that human experience determines what we see, in this case, experience with retinal projections of moving objects.

Music

By 2009, work on visual perception spanned more than a decade, including six years that I had spent as director of the Duke Center for Cognitive

Neuroscience (I had stepped down as chair of neurobiology in 2003). I was 71 by then and beginning to suffer the increasing marginalization that inevitably comes with age. My lab had never been more than seven or eight people, but by 2009, the number had dwindled to three or four. Moreover, I had begun to turn from vision to audition. There were several reasons for this change in direction, the main one being the need to verify the general ideas derived from vision in another sensory modality. Other than vision, audition was the best understood sensory system. Moreover, audition presented a database that was not only useful but fascinating in its own right: music and its poorly understood phenomenology. In vision, it had been easy enough to generate a database of natural scenes that served as a foundation for predicting what we see on the basis of the frequency of occurrence of stimulus patterns. But visual aesthetics—why we *like* one stimulus more than another—seemed a closed door. In contrast, in audition, the data provided by millennia of musical history provided the needed information to explore the basis of aesthetic appeal in a worldwide art form.

The work on music had begun around 2000 more or less for fun, motivated as well by my longstanding effort to play the guitar halfway decently. Music seemed like an interesting challenge and collaborating with David Schwartz, a newly arrived postdoc, offered an opportunity. David had been trained in psychology at the University of Michigan and had joined the lab without any special preconception of what we might do together. In discussing the possibility of venturing into audition, David, who had considerable experience in music, was game. As a result, together with another postdoc (Debbie Ross), two third-year medical students who had taken off a year to work in the lab (Jonathan Choi and Kamraan Gill), a first-rate graduate student (Daniel Bowling), and a series of undergraduate volunteers, by 2009 we had written several credible papers on music.

The aim was to test whether musical phenomena could be explained empirically on the basis of biology, vocal similarity in particular. The underlying theme was simple: given the ecological benefit of recognizing human vocalization, it made sense to think that the universal penchant for making music might be related to vocal sound signals. The general idea—which we eventually came to call "vocal similarity theory"—was that the closer a musical tone combination is to the harmonic series characteristic of human vocalization, the more humans should have evolved to like the tone combination.

By 2009, the lab had taken a break from vision and was plugging away full bore on audition and music as a way to understand some of its peculiarities. I had certainly not lost interest in vision and was carrying on some work that followed up to what we had been doing. But the grant applications I made to the National Institutes of Health (NIH) on these topics were not well received, as had been the case for a long time. Not only had the NIH come to favor applications with a clinical payoff, but the National Eye

Institute (the logical source of support for what I had been doing) was a club to which I did not belong. Older investigators who want to pursue something that is off the beaten path are rightly regarded with suspicion, and pursuing unorthodox ideas about vision and now audition and music was an increasingly hard sell.

Singapore

This was the unhappy situation in the spring of 2009 when George Augustine, a longtime Duke colleague, walked into my office with an unexpected question. By any chance, would I be interested in joining the Duke medical school recently established in Singapore as the director of its neuroscience program? George had taken the opportunity to work at the new school a couple of years earlier and was intent on filling the vacant position in neuroscience with a reasonable person, as was the dean of the school (Ranga Krishnan), and the dean charged with hiring new faculty (Pat Casey). Both Ranga and Pat had moved from Duke to take up positions in Singapore, and both were colleagues for whom I had great respect.

The rationale for Duke's venture to set up a sister medical school in Asia needs some explaining. Singapore's colonial heritage meant that, as in Britain, medical school was undertaken immediately after high school as a six-year program, quite different from the U.S. system. Ever anxious to upgrade the country's system of education, the Singapore Ministry of Education decided it would be wise to invest in an U.S.-style medical school with a doctoral component that could train clinician-scientists (an M.D./Ph.D program). This educational trajectory in medicine had worked in the United States, suggesting that this was a good way to create doctor-scientists who could bring the research more effectively from bench to bedside. Johns Hopkins was Singapore's first choice for the execution of this goal in the early 2000s. But when Hopkins failed to meet the Ministry's "mileposts" in a timely way, the deal was called off. The second choice was Duke University Medical School, and by 2005, the project was underway.

To the extent that I thought about this project at all I was, as a bystander, skeptical. But as was obvious by turn of the century, extraordinarily well-educated secondary school students from Japan, China, India, Singapore, and elsewhere in Asia were increasingly joining both undergraduate and graduate schools in U.S. universities. Many of these students would stay in the United States, adding greatly to the energy and expertise of the aging population that had immigrated to the United States from Europe in the first half of the 20th century. Indeed, I had already benefitted greatly from this influx. By establishing sister institutions in Asia and sending faculty to Singapore and other Asian countries, U.S. universities could establish their "brands" abroad, thus faring better in the competitive market for students seeking education in the United States. Duke also could off-load faculty to serve abroad who would be paid by Singapore, creating a financial benefit as well.

I understood little of all this at the time George came by to explore my possible interest. But I had several reasons for taking his question seriously. First, having lost some of its zip, my lab could be reenergized for a few more years. And George didn't waste any time in pointing out the financial benefits. As any newly hired faculty member, I would receive a generous "startup package" that I could spend on whatever research I wanted to do over the next five years. This was far more support than I could anticipate in the Untied States under the most optimistic scenario. The job also came with a generous salary by U.S. standards, along with additional allowances and prerogatives. As if all this were not enough, relocating in Singapore would be an adventure at a time when life was becoming a bit humdrum. My attractiveness to the Duke–National University of Singapore (NUS) Medical School was that I had plenty of administrative experience and should have no problem organizing a good neuroscience program. Moreover, as an "internationally recognized scientist," I would lend a measure of credibility to neuroscience at the infant school. To a considerable degree, seeking out recognized names was Singapore's modus operandi. As a city-state that was striving to join the ranks of other small countries that had major-league scientific clout, it was important to be seen as having some notable players. And, in this respect, Singapore had already done well. An early recruit to advise the government on how to proceed in its overall effort to put biomedicine on the map was Sydney Brenner. Others soon followed, and both the NUS and the NIH-like Agency for Science, Technology, and Research (A*Star) Campus were well stocked with notable expats from the United Kingdom and, to a lesser degree, from the United States.

There was, however, an obvious stumbling block. In thinking over George's proposition, I was pretty sure that Shannon was unlikely to share my openness to the possibility of moving to Singapore. One of our two daughters was living near us in Chapel Hill with one of our then three grandchildren, and our other daughter was not many hours away in Atlanta with the other two grandkids. In contrast, Singapore was about as far away as one could get on the planet, with a 24-hour plus trip that was debilitating by any standard. I was thus surprised, in broaching the subject when I came home that evening, that Shannon's response was enthusiastic. She had been planning to retire within a few years as the editorial director of Algonquin Books which she had cofounded 25 years earlier. With retirement looming and the same marginalization beginning to affect her, an adventure during which she could continue her work remotely but gradually cut the cord with Algonquin appealed to her. I think she also sensed that it would be a good thing for me, perhaps fending off the depression that she imagined might afflict me as things inevitably continued their slow decline at Duke.

I had left it with George that Shannon and I would think hard about the possibility and get back to him. We talked about little else over the next few days, coming to the conclusion that there wasn't much to lose and a good deal to be gained, at least for me. So in June 2009, we took the first of what would be many trips to Singapore, this one simply to look over the lay of the land. In truth, I am not sure Shannon or I could have found Singapore on the map and our knowledge of the island and its cultural makeup was nonexistent. But Singapore is a thoroughly modern, beautifully organized city-state in which physical dilapidation, crime, and U.S.-style poverty are virtually unknown, and it as cosmopolitan as New York or London without the ethnic tension. The only obvious downside to emigrating was the unhappiness of our daughters, both of whom were upset about our being so far away (it hadn't occurred to us that in their view we were "elderly," which no doubt contributed to their concern). Nonetheless, they eventually relented. We found a sitter for our house in Chapel Hill in case things didn't work out and, by September 2009, had packed up and were on our way.

A truism is that adjusting to Singapore is "Asia lite." A problem for any couple, however, is that while the spouse with a full-time job has some sense of purpose and is pretty well insulated from loneliness, that is not the case for the partner who doesn't have work. Although Shannon had plenty to do online for Algonquin Books, it is quite different being in a workplace and sitting in an apartment using the Internet and Skype. It was soon clear that Shannon would be condemned to the life of an expat spouse, of whom there were a great many in Singapore. Although many became good friends, it was clear from the outset that Shannon's experience would be quite different from mine.

The Duke medical school in Singapore turned out to be a plus for both for Singapore and Duke. Nonetheless, its success was achieved only after an enormous amount of work by Sandy Williams (then dean of the Duke medical school in the United States), Pat Casey, and other "pioneers" during the initial years of the project. The Duke–NUS Graduate Medical School officially opened in 2006, housed in what previously had been a barracks close to the site where the new school was being built, at Singapore's expense, and next to Singapore General Hospital with its excellent clinical faculty. Twenty-five students were taken into that first year's class and began their training in makeshift circumstances. But it worked, and in 2008, the faculty, students, and staff moved into the newly constructed school.

Despite having missed the hard part of getting the school going, my entry into professional life at Duke–NUS was not altogether easy. Everyone's best intentions notwithstanding, I had to set up a new lab and hire a new staff. The only person I brought with me from the United States was Dan Bowling, the graduate student working on music for his doctorate. Dan arrived in Singapore a few weeks before we did and was an enormous help. But the new lab had to be remodeled and new equipment bought. Money was no problem, but ordering things, many of which had to come from abroad, was not simple, and it was a good three months before we could actually get to work. In the meantime, I was learning the administrative ropes of the new school and the faculty already in place.

Both Pat Casey and Ranga Krishnan, the newly appointed dean of the school, were excellent administrators, but neuroscience in Singapore was a moving target. Ranga told me a few weeks after I arrived that, if I was willing, there was another component to the job I had signed on for, namely, becoming executive director of the A*Star neuroscience program in Singapore. A*Star was more or less the equivalent in Singapore of the NIH, which is to say a collection of research centers on its own campus. This codirectorship made a certain amount of sense, and I was curious to see another side of science in Singapore. The A*Star neuroscience director had been Colin Blakemore. Colin, however, had been in Singapore only part time, and the A*Star administration seemed glad to welcome a full-timer in this interesting if ultimately frustrating position.

Before arriving, I had begun to place ads for postdoctoral fellows and research assistants (RAs). (Even though I had signed for what could be a five-year stint, I thought it unwise to take on any new graduate students because it was unclear how long my tenure might actually be.) In this I was lucky, and before long, in addition to Dan, I had three RAs, one very good postdoc, and two more on the way. The RAs and the postdoc who came first were from local institutions, but because money was in short supply in the United States for the kind of work I was doing, postdocs from abroad were not hard to come by. And so, by the late fall of 2009, things in the lab were pretty much set to go.

Research in Singapore

Having gotten things set up in Singapore, the question once again was what to do next. There were two attractive avenues to pursue now that I had plenty of support to do whatever I wanted without having to get more grant money in the United States. The first was further understanding music in biological terms. The second was to press on with visual perception, in particular the mechanism that translated the frequency of stimulus occurrence into the qualities we actually see.

To take music first, the basis of consonance and dissonance, the rationale for scales, the universality of a few scales in music, the rationale for tuning, and octaves as a musical framework all remained largely unexplained. The challenge was to examine whether these issues could be explained in biological terms. Kamraan Gill, the medical student who joined the lab for a year in 2008, had shown that of the billions of possible scales that humans could have used to make music, only a few dozen were in fact employed. The payoff was that these few scales were empirically ranked at the top of the list when the similarity of all possible scales was compared to the uniform harmonic series that characterize human vocalization. This finding strongly supported the idea that humans prefer tonal combinations that mimic conspecific vocalization.

A second encouraging observation came from Dan Bowling's work on the expression of emotion in musical tones. It had been accepted for centuries that major scales generally are used to express happy, excited, or martial feelings, whereas music in a minor mode expresses sadness, lethargy, and a subdued state of mind. Dan showed that vocalization in these various states indeed tracked the tonal intervals found in major and minor scales.

These successes encouraged exploring further links between music and human vocalization. One possibility was looking for a parallel between the music and speech of cultures whose languages used tones to indicate meaning, such as Mandarin, Vietnamese, and Thai. These linguistic data then could be compared with the characteristics of classical music in various cultures. Singapore was an ideal place to carry out such studies because of the polyglot population and extensive library of Asian musical scores housed at the NUS music library. By good fortune, two of the research assistants I had hired, both graduates of NUS, were well prepared for this work. Han Shiu 'Er was a native Singaporean fluent in Mandarin and knowledgeable about music, and Janani Sunderarajan was fluent in Tamil and an expert in the classical Carnatic music characteristic of South India. Despite some bumps in the road, they both took to the project and were soon documenting the relationship between classical Asian musical scores in tone and nontone languages. Based on our "vocal similarity theory," the supposition was that music in tone and nontone language cultures should be quite different. And this turned out to be the case. The music of tone language cultures uses greater pitch differences than nontone languages, which use smaller intervals and less frequent reversals of pitch direction. In contrast to classical European music, these findings were common to the classical music of China, Vietnam, and Thailand.

In another study, we examined the idea that musical consonance depends on recognizing and attending to human speech. Based on the work that Gill had carried out on scales, we supposed that the attraction to tone combinations would reflect the degree to which they represented a harmonic series, and vice versa in the case of dissonant tone combinations. In music, melodies and harmonies make up the tone combinations that can be simple dyads (a combination of two tones) or more complex chords. The idea was that when a tone combination in music more closely approximated a complete harmonic series—for example, an octave or a perfect fifth—the more consonant it should be. Conversely, tone combinations that less faithfully mimicked a harmonic series—for example, a minor second or a major seventh—would be relatively dissonant. Again, this turned out to be the case, as documented in Dan's thesis in 2012 and the papers that followed from it.

About the same time, another postdoc arrived in the lab with the intention of pursuing empirical explanations in music. Brian Monson had finished a doctorate in speech analysis at the University of Utah and, as a member of the Mormon Tabernacle Choir, was well versed in vocal music. He took up a project that examined more specifically whether the same ideas that had been useful in rationalizing visual perception applied to audition. The goal was to ask whether the way we perceive basic acoustical features, such as loudness and pitch, are predicted by the empirical characteristics of speech. If trial-and-error experience is also the basis for perception of tonal sounds arising from unknowable physical sources, then one would expect the frequency of occurrence of a physical intensity or frequency (the physical correlates of sound stimuli) to underlie the loudness and pitch values we actually hear. Brian succeeded in confirming this idea by correlating the frequency of occurrence of intensities and frequencies in speech with classical psychophysical functions in audition.

Nonetheless the major preoccupation of the lab continued to be vision. The piece in the puzzle that had been left more or less in limbo when the lab moved to Singapore was the mechanism underlying the empirical association between visual experience and visual perception. The percepts we become aware of never accord with physical measurements, and the issue was how to explain this disconnection in neurobiological terms. Now that I had the wherewithal to hire new collaborators who had the talent in the needed computational domains, empirical vision joined music and speech as a mainstream in the laboratory.

The initial foray into how empirical vision might work was undertaken by a bright research assistant named Mike Hogan who was taking a year off after graduating from Hampshire College. Although what he did was entirely bootstrapped, the goal was to use artificial neural networks instructed by trial-and-error experience rather than algorithms, asking whether evolved networks showed evidence of "perceiving" visual qualities in the strange way that humans did. The best visual quality for this purpose was the lightness values seen in response to luminance patterns. Thus, Mike set about training simple neural networks in artificial environments in which reproductive success depended on responding to light intensities.

In this he was soon joined by two postdoctoral fellows, Cherlyn Ng and Yaniv Morgenstern. Cherlyn had gotten her doctorate in molecular biology and had done a postdoc in cancer research. But she was unenthusiastic about the sort of work that the field demanded and wanted to try her hand at neuroscience. Yaniv, in contrast, had already trained in neuroscience in Canada and arrived after finishing a postdoc in Montréal. He was adept at programming and what Mike had started during his year in the lab Yaniv took over with a much stronger background. The three collaborators became increasingly good at crafting a project on the perception of light intensity that began to make some sense. The idea was to use simple luminance patterns received by a sensory array that could then inform a feedforward neural network whose evolved connections and output signified the "perception" the network had chosen as a basis for its "behavior." Populations of such networks used trial and error to continually improve their responses over time without any indication of what problem they were trying to solve. I/we believed that the inability to measure the physical world using biological sensors was the major problem vision had to contend with and that this empirical approach was the only way a nervous system could deal with the intractable complexity of its owner's environmental niche.

All the while, I was of course learning a great deal about Singapore. The theme in transforming Singapore from an underdeveloped island to a major player had always been money. And it was this aspect of science in Singapore that I struggled with unsuccessfully in my role as the director of the neuroscience program at the Duke–NUS Medical School and as the executive director of the A*Star neuroscience program. In both cases, the stumbling block was freedom to do "blue sky" science, which was constrained by the government's preeminent concern with the economy. When I arrived in 2009, there was some enthusiasm for the idea that excellence in basic science would differentiate Singapore from countries wedded to human health as the goal of biomedical research. Over the four years I was in there, however, there was a decided shift from the idea that Singapore had the financial wherewithal to pursue both avenues to the view that basic research should contribute to the bottom line. The Ministry of Finance came to have increasing control over science policy, and the climate for carrying out basic science by the time I left was pretty much like every other developed country. Although I left for personal reasons, given my research, I would have had a tough time getting grants in Singapore had I stayed much longer.

What made me call it quits after four years was that Shannon was now 10,000 miles away, having returned to Chapel Hill at the end of 2012. I had no counter to her reasons for going home other than the self-serving desire to go on doing research in what for me was a still a comfortable environment. So in September 2013, I returned to Duke, where I took up more or less where I had left off four years before. The reality, however, was that I was now an elder statesman whose presence was of no particular value to a new contingent of neuroscientists and administrators.

Back at Duke

When I came back to Duke in the fall 2013, I was prepared for a less-than-enthusiastic welcome. At 75, I would have been expected to become emeritus and to quietly fade into the academic sunset. But this was something I did not want to do. I had been forewarned by Ranga Krishnan, the astute dean of Duke–NUS Medical School, that becoming emeritus was rarely a wise move. He pointed out that the only emoluments that came with that status at Duke were an email account and the right to park on campus if one could find an empty space. But in seeking some other arrangement, I found out that things were not so simple. I couldn't transfer the considerable research money left in my account in Singapore to Duke, meaning that I would be starting all over seeking grant support, long the measure of an individual's value to a department of basic science. And although I had imagined returning to the Department of Neurobiology at Duke where I had been chair for 13 years, after a decade in absentia, I had few friends there.

The Neurobiology Department had fallen on relatively hard times over those years. Jim McNamara had taken over as chair when I stepped down in 2003. As a neurologist and leading researcher on the genetics of epilepsy, he was an ideal choice in an era that had become heavily biased toward clinical relevance and grants that advanced the human health agenda. But events conspired against him. Several of the faculty members that I had hired in the 1990s were now mature scientists of considerable stature and were looking at other jobs. In addition, perhaps my most successful hire—Larry Katz—died of malignant melanoma in 2005. The combination of Larry's death, the departure of Mike Ehlers to Pfizer Pharmaceuticals and Guo Peng Fong to MIT were major hits. At the same time, David Fitzpatrick, a highly regarded vision scientist had moved on to become director of the Duke Institute for Brain Sciences. The same course was taken by Michael Platt, another excellent faculty member, a few years later when David left to become director of the new Max Planck Institute in Florida.

In all the hiring I had done at Duke and then in Singapore, I had sought entry-level scientists with promise. Although some of these hires failed, the batting average was bound to be better than trying to poach senior faculty from other institutions. Given the complications of moving, leaving children's schools behind, and distancing oneself from long-standing friendships, most senior researchers who put themselves on the market actually are trying to force their home universities to match an attractive outside offer. And most universities, unless the faculty member is a real pain in the ass, are happy to meet this demand rather than take on the far greater trouble and expense of finding a replacement. But in replacing these departures at Duke, Jim had recruited senior faculty and never hit pay dirt, and a new chair was being sought to invigorate the department.

All this transpired while I was in Singapore, but I knew that the search for a new chair had not gone smoothly. In the end, the job was accepted by Stephen Lisberger, a very good vision scientist from the University of California at San Francisco. I had never met Steve, but he had a reputation of being hard-nosed. Indeed, the only interaction Steve and I had had was his complaint several years earlier that a paper of mine he had overseen as an editor probably should not have been accepted (this was the first paper on music in 2003, and his complaint was not entirely without merit).

Although Steve never said so directly, it was clear from third parties that I would not be particularly welcome in my old department. This lack of enthusiasm was reasonable as I had noted in seeing other ex-chairs find a home: there is no joy in having someone previously in authority looking over one's shoulder, whether in fact or imagined. Thus, I probably would have taken the same view had I been in Steve's shoes. In any event, this left me stateless, so to speak, as appointments at Duke are generally made in departments. But to the credit of the search committee, Steve did an outstanding job setting the department to rights and extracting the substantial money from the university needed to do so. He hired good junior people and was deeply dedicated to the details of running the department, something that I always found burdensome and often neglected.

The solution for me finally emerged when I asked the provost, Peter Lange, what he saw as the alternatives. He pointed out that the obvious answer was to be hired in the Duke Institute for Brain Sciences (DIBS), which was then being run by Michael Platt whom I had recruited to Neurobiolgy some years earlier. As an "institute" at the university rather than a department, DIBS could hire in its own right. Michael agreed to this arrangement and gave me a small space in the Center for Cognitive Neuroscience, which was also under his aegis. I thus would be a department-less "research professor" but with full faculty standing. Because I had no grants and really didn't want to rejoin that competition, I was happy enough with the arrangement at no salary. This amorphous status served my intention to remain in the neuroscientific mix of the university, teaching and taking pokes at fatuous arguments in seminars (not a wise priority, but one that I had always enjoyed). And there was a lot of science still to be finished up with my erstwhile collaborators from Singapore.

Having resettled, the first order of business was to establish courses in the two domains that remained my interests, music and vision. A new fashion in teaching had taken hold by 2013 was massive open online courses (MOOCs) and Duke had already partnered with Coursera, one of the major players in this new way of educating. The idea of presenting material on vision and music for free to a worldwide audience was immediately attractive. My first effort in 2013 was a MOOC on vision, with the goal of putting together a course based on a book that Beau Lotto and I had recently written (*Why We See What We Do Redux*, Sinauer, 2011) whose message would be relatively easy to convert into an online course. Thus, I enlisted two savvy undergraduates who knew enough about the video editing software to put together a beta version of the course on our own (a year later, I redid the course with professional help). Having tested the waters, I did the same thing for music, coupling another MOOC with a book on music I was then writing.

Not writing grants was a huge relief after 45 years of begging for money in an increasingly unfavorable environment for people like me who were interested in issues outside the mainstream. Although lacking grants meant that any new work had to be low cost (as indeed much of it already was in Singapore even when the lab was well heeled), this was no great impediment since I could tap into a sizable slush fund that had accumulated over the years. One order of business was to finish up Yaniv Morgenstern's project, showing that the same ideas explaining the relationship between light intensity and the perception of lightness also applied to the relationship between spectral distribution in color perception. At the same time, Yaniv extended the work on lightness based on the experience of evolving neural networks. These papers were published in 2014 and 2015 and were backed up by a more general account of this overall theme coauthored by Yaniv and Bill Wojtach.

Another piece of unfinished work from Singapore was a theoretical paper written with Chidam Yeggapan on the geometrical basis of color vision. The gist of Chidam's argument was that solving the four-color map problem in a 2-D image on the retina was basically a geometrical challenge. In a 2-D space, the evolution of color vision must contend with the four-color map problem as it pertains to light spectra in images. At the same time, color vision must be able to identify all spectrally different equiluminant points on a 2-D plane. These dual goals can be achieved by two pairs of direction vectors that give rise to four color classes defined by four unique hues that are pair-wise opponents. Despite its complexity, I thought Chidam's paper was both ingenious and correct. Nevertheless, the paper proved to be almost impossible to publish despite its originality—or perhaps because of it—and was anonymously rejected by all of the first-line vision science journals we sent it to. It was not until 2016 that this work saw the light of day in a newly minted vision journal that was no doubt anxious to take any paper by credible authors.

Another piece of unfinished work in vision was binocularity. Cherlyn Ng had begun to explore the idea that there might be a simpler way to explain fusion, stereopsis, and the puzzle of ocular dominance. Uniting the right- and left-eye views usually was tackled in terms of matching corresponding image points, although exactly how this could be accomplished remained debatable. Another possibility was that different levels of activity at anatomically corresponding retinal points were being used to produce a sense stereoscopic depth. Once again, this work proved difficult to publish.

There was much to finish up on music as well. Dan Bowling and I undertook a short review that summarized work on the hypothesis that consonance and dissonance were intimately related to the biological advantages of recognizing and attending to the uniform harmonic series that characterize human vocalization. The initial intent was a more extensive article that would pull together all aspects of musical tones. But Dan and Kamraan Gill argued correctly that more evidence was needed, particularly with respect to musical chords. Although consonance and dissonance had long been studied in the context of dyads (i.e., musical intervals consisting of a lower reference note and a higher tone), there was almost no work on higher-order chords. This deficiency led to a further project on triads and tetrads, the three- and four-tone chords familiar in musical harmony. Dan had begun this work in Singapore testing musically literate and naïve subjects on their relative attraction to musical chords. But there was much more to do and, without any particular help from me, the two of them forged ahead and analyzed a large set of three- or four-note chords with respect to their appeal to listeners and their physical similarity to a harmonic series. This work was published in 2019 and Dan, now at Stanford, and I are still trying to understand musical tuning in biological terms as I write this.

Summing Up

To go back to the beginning, the foundation for thinking about the nervous system when I was a first-year medical student in 1960 was primarily knowledge about nerve cells and neural signaling based on work carried out over the preceding few decades by Hodgkin, Huxley, Kuffler, and Katz with their collaborators and students. This remarkable body of research had led to a reasonable understanding of how information in the nervous system is transferred by action potentials and conveyed to other neurons by synaptic transmission. Although a wealth of detail about these processes has been added since, this basic understanding of neural function at the cellular level remains much the same as when I first learned it.

In contrast to the clarity of what is known about neural signaling, the functional significance of brain structures, their complex interconnections, and how they determine human behavior remains poorly understood. Why, then, despite the enormous increase in information about the properties of neurons in different regions, their connectivity, their transmitter pharmacology, and the behavioral situations in which they become active, do neuroscientists remain relatively ignorant about perception and other higher-order behaviors that now interest us most?

The reason, at least in part, is the absence of some guiding principle or principles that would help sort out the neural underpinnings of perceptual, behavioral and cognitive phenomenology. One doesn't have to be steeped in history to recognize that other domains of biological science have typically advanced under the banner of some overarching framework. The complexity of the human nervous system notwithstanding, when all is said and done, our brains and the rest of our nervous systems are arguably doing just one basic thing: using trial and error to associate sensory information with successful behavior by neuronal connectivity. As a result, the neuronal associations underlying successful behavior in response to stimuli wax over the eons whereas unsuccessful associations wane, eventually leading to the brain circuitry humans and other animals have today. By the same token, modulating neuronal connectivity by activity-dependent plasticity promotes learning during the lives of individuals. All that is needed to implement these strategies is plenty of time and a way of providing feedback about the relative success of behavior. The history of life on earth has provided ample time and natural selection has offered a wonderfully powerful mechanism for assigning credit to successful behavior.

At 82, I have not quit promoting this explanation of nervous systems. Brains seem to be logically unfathomable skeins of neuronal connections that embody the ever increasing empirical associations that have kept animals going strong for more than 500 million years and counting.

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