Margaret Stratford Livingstone

Born:

Danville, Virginia
April 3, 1950

Education:

Massachusetts Institute of Technology, Cambridge, MA, Biology, BS (1972)
Harvard University, Cambridge, MA, Neurobiology, PhD (1981)

Appointments:

Visiting Fellow, Princeton University (1981–1983)
Research Fellow in Neurobiology, Harvard Medical School (1982–1983)
Instructor, Harvard Medical School (1983)
Assistant Professor of Neurobiology, Harvard Medical School (1983–1986)
Associate Professor of Neurobiology, Harvard Medical School (1986–1988)
Professor of Neurobiology, Harvard Medical School (1988–2014)
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Honors and Awards:

Phi Beta Kappa
Presidential Young Investigator Award, 1984
NIH Research Career Development Award, 1985
Office of Naval Research Young Investigator Award, 1986
Mika Salpeter Lifetime Achievement Award, 2011
The Caroline P. and Charles W. Ireland Distinguished Visiting Scholar Prize, 2012
The Grossman Award from the Society of Neurological Surgeons, 2013
Roberts' Prize for Best Paper in Physics in Medicine and Biology, 2013

Margaret Livingstone has studied the role of monoamines in lobster behavior and in learning in fruit flies, but for most of her career, she studied visual processing. In collaboration with David Hubel, she revealed the interdigitating parallel nature of the visual system. In 1984 they described a new subdivision in primate primary visual cortex involved in processing color, and described the anatomy and physiology of this previously unknown system. Her laboratory showed that macaques, like humans, have specialized regions of the temporal lobe that are selectively involved in face processing. She has explored the ways in which vision science can understand and complement the world of visual art.

Margaret Stratford Livingstone

Early Years

I feel silly writing my 'biography' because I don't feel done yet, and I can't imagine why anyone would want to read it anyway, so I am going to imagine I am writing to a young person, I hope a woman, who is thinking about a career in neuroscience. My route to becoming a neuroscientist has been haphazard, and if a young person has the sense to be reading the biographies of established neuroscientists, they already know more than I did until I was halfway through medical school. I have included some personal history that I was inclined not to, because I know that the question of what kind of personal life you can have as a scientist looms large for many women, and I am proud of being a single mother and doing good science. I have also revealed how uncertain I have felt at times, to help dispel the notion that you have to be a genius to succeed in science. I have always felt, and still do, like an amateur amongst experts, but I think knowing that you don't understand something that you find fascinating is a good place to start if you want to do good science; I wish I had been more comfortable when I was younger with feeling mystified. If you finish this essay and think "I could do that, but I wouldn't have been so naive, or disorganized, or I wouldn't have put up with that," then this exercise will have been worth it.

I was born in Virginia in 1950, but my family moved almost yearly. My father rose through the ranks of an insurance company, and every time he got promoted, we moved, because it was thought bad policy to promote someone to a position above a previous colleague. Relocating employees of large companies was common practice in the 1950s because wives and families were considered subordinate to a man's career. So I was always a new kid, and usually had the wrong accent. When I try to understand how I came to do science, I suspect that my not fitting in socially was a factor. Before I went to college we lived in Danville, VA; Leaksville, NC; Draper, NC; someplace in South Carolina; Charlotte, VA; Atlanta, GA; Norwalk, CT; Arlington Heights, IL; Roanoke, VA; and St. Petersburg, FL. When we moved to Connecticut I was in the first grade, and had to go to special speech classes, because they thought my southern accent was a speech defect. It took my parents months to realize that I didn't actually have a speech defect because my father was in a new job and my mother had to deal with moving

and a new baby. We moved when I was a freshman in high school and halfway through my senior year in high school. I was insecure and socially inept.

Our present culture and mind-set are so different from what I grew up with that I want to try to describe what it was like in the 1950s in the Southern United States. It was not a great place to be a smart girl, and I know it was an even worse place to be a minority, though I was largely unaware of those issues. I never felt like being smart was socially acceptable, but I studied hard. I was not popular though I deeply wished I were; I do not know if I studied to compensate, or whether I was unpopular because I studied. Science was not interesting in the schools I attended; it consisted mostly of memorizing lists of phyla and species. I liked math, but none of the high schools I attended offered anything beyond basic algebra. I did collect skulls that I found and made skeletons from road kill by soaking the carcasses in lye, but it never occurred to me that I should aspire to do anything except become a wife and mother. My original impetus for studying science, and eventually engineering, was that I worried I wouldn't get married—I didn't seem to be particularly attractive to boys, so I figured I would need a job to support myself.

I wished I could be a cheerleader, but the unwritten rule was that only popular girls could do that, so I didn't even try. I took three years of home economics because it was required (of girls; boys took shop), and learned, in school (!), to cook, sew, and keep house. I remember a lesson in which we were taught not to keep our nails too long because they would snag on our stockings and not to have a windblown hairdo because it looked messy. I also learned, in those home-ec classes, to let boys do the talking, and how to ask questions that would "bring him out." Jim Crow laws were in effect, and I had been told that as white girl I was supposed to use the bathroom labeled "ladies" not "women." Water fountains were labeled explicitly "white" and "colored." It is amazing to me now that I accepted all these customs as reasonable, but all the people around me, especially adults, certainly did. Billy Graham, the evangelical preacher, was a local celebrity who visited our high school and gave sermons in the auditorium. We pledged allegiance and said the Lord's Prayer every morning in class. Church was socially very important, but I had trouble reconciling logic with religion, and refused to go, even though it made me still less popular. Big hair was in; I slept nightly on two-inch rollers with bristles! My junior year I finally had a boyfriend, but he broke up with me after he found out my PSAT scores were higher than his. My second boyfriend was socially above me and was regularly an escort at Debutante balls, to which I was not invited, not being FFV (first families of Virginia). Dates were invariably to drive-in movies, or to drive endlessly, in circles, around the Shoney's (a local hamburger place). I can't imagine why we did this, but I was thrilled to be included.

Young people today would be horrified by the blatant sexism and racism that were the norm in the culture I grew up in, yet the main reason I thought

so much outside the box was because I didn't fit in. I feel very lucky to have ended up in science despite the social pressure not to. I had read widely enough to realize (contrary to the pervading local culture) that people of color should be equal to whites, but I assumed the practice of "separate but equal" was fair, until I read a *Life* magazine story that showed the reality of that policy. Similarly, reading Betty Friedan's *The Feminine Mystique* in my late teens made me realize that I had more choices than I had thought. My mother had a college degree, and loved math and science, but she worked for only a few months after college before becoming a housewife, because that's what everyone she knew did. She often told me she regretted not working, though she said being a wife and mother was completely fulfilling; she said she didn't mind playing a supporting role because she thought my father was the most brilliant and wonderful man in the world. My father always called me his "first born," but my younger brother his "son and heir." He encouraged me to aspire to go to a good college, but we both assumed I would get married and be a housewife.

I started high school in North Caroline, moved to Virginia, and then, in the middle of my senior year, to Florida. In all three schools, obligatory pep rallies were a regular event, in which the entire student body crowded into a hot auditorium the day of some sporting event to cheer and chant and pray in unison. I abhorred pep rallies, and I still cannot abide spectator sports. By moving so much, I managed to hit 3 consecutive years of state history classes, in three different Southern states, so I know more about the War of Northern Aggression than you can imagine. When I moved to Florida in my senior year, I had to take two semesters of "Americanism vs. Communism" in a single semester because an entire year of that subject was a state requirement for graduation; the textbook was J. Edgar Hoover's *Masters of Deceit*. That last move was particularly devastating because I had finally settled in socially in Virginia, and even had a boyfriend. I tried to convince my father to let me stay in Virginia to finish my senior year, but my mother was dying of a glioblastoma, and my father needed me to run the household.

College Years

Florida was horrible. Only a few students in my class planned to go to college, and those who did planned to go to the local community college, except two or three of the smartest kids who wanted to go to Florida State. To go to an out-of-state college was unheard of. I had applied to and was accepted by three colleges before we moved to Florida: MIT, Cornell, and Duke. My Florida guidance counselor did not know what the initials M.I.T. stood for. I was so shook up by moving, and by my mother's illness, that I chose to go to Duke rather than MIT because MIT terrified me, and Duke was where my

mother had had her brain surgery. I acquired a new boyfriend who worked in a gas station and, in retrospect, was not very nice to me. It was a relief to leave home to go off to college, even though there was a need for me to stay home and take care of my three younger siblings and my very sick mother.

At Duke, I enrolled in the Engineering School because I thought as an engineer I could support myself and would not need a husband (I was still insecure about the possibility that I could attract a husband), and because it seemed like a good major for someone who liked math and science. This was 1968. Drugs and protest hit the Duke campus like a tidal wave. Classes were boycotted to protest the Vietnam War (I am still unsure about the logic of this since most of our parents were paying a lot of money for us to attend Duke). It seemed like everyone was marching, protesting, drinking, doing drugs, and having sex. Nobody much cared about classes, except to a small extent at the Engineering School. I had to take mechanical drawing and materials science. I learned a lot about cement and metal fatigue, but I found it boring. I got a job as an engineer with the Army in Washington, DC (the only summer job I could get as a student engineer) and was supposed to help design bullets (shells?) that would "long time out." That is, if they failed, they would blow up at the end of their timer, not the beginning. I don't think I did anything useful engineering-wise that summer, and I didn't like working as an engineer. My two male supervisors took me and some visiting dignitaries to a strip bar one evening, and I didn't like that either, but it never occurred to me to object.

I decided that I had made a mistake by not going to MIT, so I applied to transfer for my junior year. I am now pretty sure that in the late 1960s Cambridge was just as crazy as Durham, but I didn't know that. I was just as crazy as everybody else, but I had had enough of beer and drugs and sex and thought maybe there was something else I might get out of college. The whole country was nuts then. I think that the craziness of the country during the 1960s was more a phenomenon of demographics than politics. The largest cohort of people in the country, the baby boomers, hit their teenage years then and got overwhelmed by hormones, so I think our whole culture became dominated by us and our adolescent behavior. It really was an astonishing time.

When I arrived at MIT, I was depressed at first because it was cold, dark, and wet, and the classes were really, really hard. It was the first time in my life I had assignments that required thinking, rather than memorization and practicing what I had been shown how to do, but it was absolutely exhilarating. I took introductory biology from Salvador Luria. His lectures consisted of telling us how he and his friends had worked out the principles of microbiology. Our tests challenged us to design experiments to figure out something unknown. Boris Magasanik taught the next semester. I was hooked. Then I took biochemistry from Gene Brown who told us how he and his colleagues had deduced each step in the Krebs cycle. I loved MIT. All

the women lived in one dorm, McCormick, so the number of women at MIT was limited by the number of rooms there—35 women (in all of MIT) when there was only one McCormick tower, and 70 when they built the second. The women at MIT were astonishing. Although reading Friedan had made me realize that I could work instead of getting married,[1] at MIT I found brilliant women who thought they could do anything. They thought they could do what they enjoyed and found interesting. My favorite classes were biology and biochemistry, probably because the teachers were so enthusiastic and interesting, so I decided to go to medical school, largely because I somehow got the idea that medicine involved research. I am not sure why I thought this, but I did. I was accepted at Stanford and Harvard Medical Schools, but because Stanford sent me a letter saying that they were accepting a disproportionate number of women in order to address the dearth of women in medicine, I went to Harvard. Stanford really could have put it better.

I loved the first two years of medical school, except biochemistry, in which we had to memorize the Krebs cycle, which was much less interesting than it had been learning from Gene Brown how they had figured each step out. I understand that premeds have to memorize all of intermediary metabolism in order to even get admitted to med school these days. I think that is unfortunate. I loved physiology, anatomy, and histology. I took neuroanatomy from the great Walle Nauta, who, using the Nauta method, had worked out most of the tracts in the spinal cord and brainstem. After a whole semester, though, of neuroanatomy from 8 A.M. to noon on Tuesdays, Thursdays, and Saturdays, we only made it as far north as the midbrain. Years later, I met Walle at a conference, and he remembered me as the girl with narcolepsy.

We didn't get sent to the clinic until after two years of "basic sciences," and there I was not so happy. I felt too much the distress of the patients and their families, as they were undergoing one of the worst times of their lives. The emotional stress made it hard for me to think logically. I felt frantic. I did rotations in medicine and obstetrics, and then neurology. I took neurology at Boston City, the last year that Norman Geschwind was chair. I loved that: we spent most of our time talking about how to diagnose what was wrong with someone by doing clever neurological tests. I remember one epilepsy patient whose locus the house staff could not diagnose (this was before MRI), though they suspected the temporal lobe. The patient did not show any of the classic signs of temporal lobe involvement (aura, interictal hypergraphia, or hyperreligiosity), but NG carefully questioned the patient and discovered a suitcase full of drawings under his hospital bed, so the locus was in the temporal lobe, not that it made any difference to

[1] Doing both was not an option as far as I knew.

the patient. Then I did a rotation in psychiatry at Mass Mental. Again, we talked endlessly about how to deduce what was wrong with someone's brain by talking to them and asking them to do simple things. I was mesmerized by a talk Joseph Schildkraut gave about the (then-novel) idea that dopamine might be involved in schizophrenia: the efficacy of drugs that block amines in ameliorating psychosis, the complementarity of schizophrenia and Parkinson's disease, the Parkinsonian symptoms of antipsychotics, and the psychotic symptoms that could be a side effect of Parkinsonian drugs. He provided all kinds of indirect yet converging evidence. It was like a detective novel. I decided I wanted to get a PhD and discover how to make drugs that modified aminergic circuitry. I asked the pharmacology department at Harvard if I could do a thesis on synthesizing monoamine-oxidase inhibitors, and I spent a year messing around and not accomplishing anything. Then I asked Ed Kravitz in the Neurobiology Department if I could study what monoamines actually did in his lab.

The Department of Neurobiology

The department was fantastic. There were two elderly Hungarian men: one was the chairman, Steve Kuffler, and the other was the guy who delivered the mail. For the first few weeks, I had the two of them mixed up. We had lunch seminars where the "young Turks," David Van Essen, Jim Hudspeth, Darwin Berg, and Eric Frank, used to pepper every speaker with so many questions that they never finished what they came to say. My first course in the department was some kind of neurophysiology class, and I was so overwhelmed by how much the other students knew that I went to one of the teachers, Ann Stuart, and asked her if she thought I should drop out of science. She wisely said no, that some students are just better than others at sounding smart, but it doesn't make them better scientists. (I am afraid it is a talent that I still lack, and one that is useful for getting grants.)

Ed put me on a project looking for serotonergic neurons in lobsters. I incubated bits of lobster tissue in radioactive serotonin precursor, then used paper electrophoresis to migrate small charged molecules, like amines, along the paper. I had marked where serotonin would end up by staining for nonradioactive serotonin in the "hot zap." I cut out the spots from the different tissues where the serotonin should be and counted them in the scintillation counter. Several were quite radioactive, but I had not yet got the concept of a baseline so I had to go back and repeat the experiment, cutting up the entire strip of migrating radioactive stuff from each tissue, and this time comparing the spots to the rest of the strip. I did find out where serotonin was made in the lobster, but that didn't excite me. I wanted to know what it was doing in the overall behavior of the animal. I asked Ed if I could just inject amines into some lobsters to see what would happen. Ed had been studying himself for some time what serotonin and octopamine

(the lobster equivalent of epinephrine) did at the lobster neuromuscular junction, and, since both amines made the thumb muscle of the lobster tonically contract, Ed said no, I couldn't do that experiment because the lobster would just contract all its muscles.

Ed used to take his entire lab to Woods Hole every summer, so that summer I helped pack everything up and schlepped it all down to the Cape. Because so many labs there study lobsters, there were a lot around, and a member of another lab let me have six lobsters to try out my experiment of just injecting amines, which I had been yearning to do for months. I put yellow bands on three lobsters and red bands on the other three. I injected the yellow-banded lobsters with some octopamine (about a pinch as I recollect, dissolved in seawater), and the red-banded lobsters with some serotonin. In a few seconds the red-banded lobsters all rose up on their hind legs and spread their claws high and wide; the yellow-banded lobsters all raised their tails, lowered their heads to the ground, and spread their claws forward, as if they were bowing. You didn't need to know anything about lobster behavior to realize that the red lobsters were in an aggressive pose, and the yellow ones submissive, though I did happen to know those were typical postures for aggressive and submissive lobsters. The lobsters were not acting aggressively and submissively, though; they were just frozen in those stereotyped postures. So I went and found Ed, and brought him back. The six lobsters were still frozen in those opposing postures. Ed was impressed and admitted that he had been wrong not to let me do the experiment. He then said that he would get a postdoc in the lab, Ron Harris-Warrick, to do the physiological studies to find out why the two amines would have such interesting opposite effects. I asked if I could do the physiological experiments, and Ed said, no, Ron knew how to do physiology, and I was a chemist (after only a year I was a neurochemist!), and I needed to finish the project I had started, proving that the cluster of cells I had found really were serotonergic. I didn't like that boring project, and I wanted to do physiology, which seemed a lot more fun than neurochemistry. But I did what Ed told me to, resentfully, and Ron began intracellular recording from various neurons in various ganglia in the presence and absence of octopamine and serotonin. Ron observed that some neurons fired more, some less, and some didn't change.

Meanwhile, I read a lot of papers about invertebrate command circuits that were responsible for complex but stereotyped behaviors, like escape. I read about sustained responses in these command circuits, and learned that, although the neurons were mixed together in the ganglia, flexor and extensor axons exited out of different nerve roots. I realized I could use this anatomical quirk to find out whether serotonin and octopamine induced these postures by activating command circuits, but Ed wouldn't let me do physiology, so one day I asked a professor from the physiology department if he had any recording equipment I could borrow. Elwood Henneman kindly lent me a polygraph, the kind that is used for electroencephalography (EEG).

It wasn't a fancy intracellular physiology rig, but it would record, with ink pens on a long piece of paper, squiggles that varied with the extracellular signals from the nerve roots. I bathed a lobster nerve cord in serotonin, and the squiggle from the nerve root that supposedly carried flexor activity got thicker; then when I bathed the cord in octopamine, I saw more activity from the extensor root. That meant that serotonin probably activated an entire flexor circuit, and octopamine the inverse. I showed Ed. Ed finally told me I could work with Ron on this project and that we could use a real physiology rig to measure activity in flexor and extensor circuits. We did not work well together. Once we were shoving each other aside trying to solder something together, and a blob of solder sank into my finger. I still have the scar. Ron said it served me right for being so pushy.

We did eventually get a nice paper out of this (Livingstone et al. 1980), showing that an entire flexor circuit was activated by serotonin, and an entire extensor circuit by octopamine, in both lobsters and crayfish, and this result suggested that monoamines could differentially modulate behaviors via differences in the distribution of amine receptors on functionally distinct neuronal circuits. Just today I heard Ed give a lovely talk on monoaminergic modulation of stereotyped aggressive patterns of behavior in fruit flies.

I got interested in the role of monoamines in learning. I had been following Eric Kandel and Jimmy Schwarz's work on Aplysia, showing that serotonin provided the reinforcement signal for fear conditioning. And there was a lot of stuff being published about monoamines acting through second messengers, like cyclic AMP. So I got the idea that monoamines could trigger second messengers, and that this would somehow lead to changes in synaptic strength. Chip Quinn from Princeton gave a lunch talk in our department about the learning mutants he had isolated in Drosophila. He gave convincing evidence that flies could show associative learning, and that there were mutants who either couldn't learn or forgot rapidly. I asked if any of these learning mutations affected monoamine synthesis or second messenger pathways. He didn't know, but he was happy to have me come be a postdoc in his lab and test his learning mutants for defects in monoamine/second-messenger pathways (I was, after all, a neurochemist).

I wanted to finish the few months I had left of medical school, and then I planned to go to Princeton to work in Chip's lab. The minimum clinical requirement for graduating with an MD from Harvard Medical School at the time was medicine (three months), surgery (two months), and three one-month rotations. I had done medicine, neurology, obstetrics, and psychiatry, so I assumed I only had to finish two months of surgery and then I would get my MD/PhD. I went to the dean of students, Dan Federman, to schedule my last rotation. His office was full of boxes of books. He said the books were a textbook of medicine he had just written and asked if I wanted to buy one. They cost hundreds of dollars. I said no, thank you, I did not plan to practice since I wanted to do research. He asked, why, then did I want

an MD? I said I wanted to do biomedical research and that an MD might be useful. When I asked about finishing my MD with a rotation in surgery, he said I had been away from the clinic so long (four years) that I really needed to do two more years of clinical rotations in order to qualify for an MD. I argued with him, but the best I could get him to concede to was another full year of clinical rotations before I could graduate. I am still astonished that a single person could have so much say over a student's career, but this was before committees, and before the formation of an MD/PhD program with set requirements. I was devastated and decided reluctantly to forgo the MD in order to start my postdoc, because I was so excited about the experiments I wanted to do. My father, who had paid in full for two and a half years of Harvard Medical School, was furious that I wasn't going to finish my MD and that Harvard had changed the requirements on me. He wanted to sue Harvard. He came up for my PhD defense, fuming. At some point Steve Kuffler took my father out into the hallway to talk, and after that, my father didn't complain ever again about my decision.

Postdoc I: Princeton

I went to Princeton, and set up a mini neurochemistry lab. As usual, I borrowed, confiscated, rescued, or constructed most of what I needed. By then Duncan Byers had discovered that the learning mutant Dunce had a defective cyclic AMP degrading enzyme (Byers et al. 1981), which was entirely in line with my ideas of monoamines and second messengers being involved in associative learning. I figured out how to assay cyclic AMP and determined that another learning mutant, Rutabaga[2], had a defective calcium-dependent cyclic-AMP-generating enzyme (Livingstone et al. 1984). It seemed that an enzyme that could link neuronal activity via calcium with monoamine reward responses ought to be a key player in reinforcement learning. We also found that a mutant that couldn't make dopamine also was defective in learning (Livingstone and Tempel 1983). Thus, three Drosophila mutants that couldn't learn had defects in the monoamine/second messenger pathway. I was thrilled.

Postdoc II: Back to Harvard

I wanted to study the effects of monoamines in mammals. When I was still at Harvard, I had gotten to talking with David Hubel about the visual system, and I decided to do a second postdoc with David to see if monoamines would modulate activity in the visual cortex. The most sensible way to do this would have been to iontophorese monoamines onto the visual cortex while recording

[2] Chip's learning mutants were named for vegetables. He wanted to name them for famous stupid people, like Lennie (in *Of Mice and Men*), but Seymour Benzer wouldn't let him.

from neurons and mapping their response properties. We didn't know how to iontophorese, but David did know how to put stimulating electrodes in different locations stereotaxically, so we decided instead to stimulate monoaminergic loci in the brainstem. We chose the locus coeruleus (LC) because it is a major noradrenergic nucleus, and we thought that stimulating the LC ought to flood the cortex with norepinephrine. We certainly observed changes in the visual cortex when we stimulated the LC, but we also noticed that every time we stimulated the LC the EEG went flat. We monitor EEG to make sure the animal is anesthetized. Normally a flat EEG means the animal is awake, whereas in sleep or under anesthesia the EEG is wavy. So we decided that maybe the differences in visual responses were due to differences in sensory processing between waking and sleeping. Since there was emerging evidence that monoamines were probably important, maybe essential, in controlling waking and sleeping, this seemed like a great thing to pursue.

We decided to study the differences in visual cortex physiology between waking and sleeping. To do this we set up cats for chronic recording (i.e., we implanted headholders beforehand under anesthesia) and recorded from them subsequently as they cycled between waking and sleeping. We saw much stronger visual responsiveness during waking compared with sleeping, not because responses were reduced during sleep, but because the neurons became very noisy during sleep. In particular, we saw large variations in firing that corresponded with the waves in the EEG, suggesting that the waves in the EEG are made up from synchronized firing in a lot of neurons (Livingstone and Hubel 1981). One of our cats did not fall asleep, after many hours, even though cats usually sleep a lot. So, thinking we knew what we were doing, we gave the cat a dose of diazepam (Valium) to make it drowsy. It had the opposite effect, which we later discovered had been previously observed—that diazepam has a paradoxically alerting effect in cats. So there we were for 12 more hours with that wide-awake cat. During that endless experiment, I read a book I found on David's bookshelf to pass the time: *Sociobiology* by E. O. Wilson. The experiment was a failure, but the book was fantastic.

One of my postdocs makes fun of me because I spend a lot of time making things for experiments. I just spent half an hour using zip ties to mount a drilled-out sawed-off Tupperware container inside a standard monkey chair to adapt the chair for baby monkeys. (It works great.) I would feel silly about this, except I remember that the first time I really impressed David Hubel was when I made a cat-sleep-deprivation apparatus from a 4-foot diameter cardboard drum I had found at the demolition site of one of the Harvard Medical School buildings. I also remember that after we had used this huge drum to sleep deprive a cat, we took it into the men's room to empty it into a toilet. It was bigger than the stall, and it was so awkward to aim at the toilet that I started laughing and couldn't warn David, who was on the far side of the drum, that our aim was off. We both ended up with soggy cat excrement

all over our feet. David used to spend hours in the lab making stuff too, using whatever he could find. He was more skilled than I am, though, and he actually machined things. My lab still thinks it is peculiar that I spend so much time building things and doing experiments myself, but it's so much fun I can't imagine not working this way. I also analyze my own data now, but I am not nearly as good as my postdocs since I didn't even begin learning MATLAB® until I was 50. I am just now, at 65, trying to master UNIX. Learning to program late in life is challenging.

The Blobs

David and I decided to try a new technique, using radioactive 2-deoxyglucose (2-DG), which is taken up by active neurons but isn't metabolized, so you can use autoradiography to identify active regions of cortex. The problem with 2-DG is that you can label only one kind of activity, because you have to kill the animal to do the autoradiography. You therefore can't contrast one kind of activation with another. So David and I tried using tritiated 2-DG for one stimulus condition and ^{14}carbon labeled 2-DG for a second condition, so that we could contrast two patterns. We could then cover the sections with Saran Wrap, and use X-ray film to visualize the ^{14}C pattern (^{3}H does not penetrate Saran Wrap), then once we had the ^{14}C pattern, we could dip the same slides in emulsion and visualize the ^{3}H pattern. This worked pretty well, but the exposures took months, and you had to titrate the two radioisotopes carefully or one would dominate the other.

While I was a graduate student, Charlie Gilbert, David Ferster, Mary Kennedy, and I shared a house in Brookline. Later on Josh Sanes moved in. It was great fun, and we had endless fascinating scientific discussions and wonderful dinners, since both David and Charlie are superb cooks. Mary and I generally chopped things and cleaned up, though she had mastered an excellent spaghetti carbonara. One day David Ferster and I were waiting on Charlie, in Torsten's lab, to go home with us, and I noticed a tray of histology slides on a bench with very clear dark and light stripes in V1. I asked Charlie why there were stripes, and he said he didn't know, because the slides had been stained for horseradish peroxidase (HRP), which Charlie and Torsten used to visualize the anatomy of single cells they had recorded from. Charlie guessed that the monkey must have had damage to one eye, but didn't know why that should turn up in this stain for HRP. I mentioned this to David Hubel, because I thought it might be a good way to visualize ocular dominance columns. David remembered that Margaret Wong-Riley had sent him a letter with a slide showing that another similar histological stain for the enzyme cytochrome oxidase also showed ocular dominance columns, in animals in which one eye had been damaged or shut, but also showed a regular pattern in normal animals, with regular puffs of cytochrome-dark staining in the upper layers of V1. David had never learned to

do histology himself, so he asked his grad student, Jonathan Horton, to see if he could get Margaret Wong-Riley's (1979) stain to work. Jonathan did, and saw a dramatic pattern in tangentially cut sections. David wanted to use our double-label 2-DG technique to see whether the dark blobs represented one orientation or another, or all orientations, so we started dipping and staining and getting very confused because the blobs seemed to light up no matter which orientation we used. We decided that this question would be best answered the slow, hard way, by recording from cells in long tangential electrode penetrations, and later reconstructing the histology. I can remember laying out huge (4-foot wide) photographic prints of cytochrome-oxidase stained sections and trying to determine where we had recorded which cells. Jonathan thought that he ought to be doing these physiological experiments, and I can certainly sympathize with his point of view, but in the end, he did a lovely study that was completely independent (Horton 1984).

David and I discovered that the cytochrome-dark regions were full of color-selective cells, but the surrounding lighter regions were orientation selective. We discovered this because David always said, "If it won't respond to a white bar, try black. If black doesn't work, try red." The color selectivity of the cells in the dark regions (we called them "blobs" because they were roundish) was striking and always fun to play with. It is very satisfying to deduce that a cell that at first is just barely responsive to a bar of light is selectively excited by blue and inhibited by yellow, or the reverse. I guess we all do science because we like figuring out mysteries, and each neuron's selectivity is a little puzzle that you can solve, usually in just a few minutes. And you do it by waving a spot of light on a screen that you can see, and you listen to the firing of the cell by putting the electrical signals that the neuron generates through a loudspeaker. There is this real-time exploration of what the cell "wants." The fact that these color cells were clustered into anatomically distinct regions was actually a rediscovery of something Charlie Michael had previously reported in 1981, namely that color cells in V1 tend to be organized in columns, but he didn't have cytochrome-oxidase staining to anchor his physiology.

We found that cells in the blobs generally responded to color and didn't care about orientation, but cells outside the blobs were the reverse. David was somewhat chagrined that he and Torsten had not noticed the existence of these blobs, and we discussed the various reasons. So, when writing up this study, I, tongue-in-cheek, wrote a paragraph to speculate on why no one might have stumbled on this before:

> The historically minded reader may have wondered how so prominent a group of cells could have been missed by so prominent pair of investigators (H&W, 1968, 1974). We, of course, wondered the same thing and can think of several possible reasons. (1) Injured cells become sensitive to almost any visual stimulus. . . . (2) With

> no anatomical indication of nonhomogeneity in the upper cortical layers, it would have been easy to dismiss occasional, apparently sporadic groups of unoriented cells. (3) A sudden series of monocular unoriented cells could be interpreted as entering layer 4C, which occasionally might have seemed remarkably superficial. (Livingstone and Hubel 1984a, p. 315)

Then I passed the (by then enormous) typed manuscript back to David who worked on it for a while, then gave me his corrected version. I still remember falling off my chair laughing when I read what David had added: "(4) The prominence was ill-begotten."

Using Equiluminance to Dissect Where and What

After recording from a lot of visual cortex, we came to realize that color and motion were not usually coded by the same cells: individual cells either cared about color, or about motion, but hardly ever both. Color and orientation tuning (shape selectivity) were also separated, though not as extremely as color and motion. Then we saw a demo that Patrick Cavanagh had made at a meeting for Vision Scientists. This was the dawn of personal computers, when a computer demo was novel, and this one really wowed me: Patrick had made a moving wheel with spokes that he could modulate from luminance-contrast to color-contrast-without-any-luminance-contrast (equiluminance) (Cavanagh et al. 1984). The motion of the wheel seemed to almost stop at equiluminance. I was so impressed by this demo, because it said to me that our perception of motion is basically colorblind, which was completely consistent with what David and I were seeing physiologically. I extrapolated to the idea that maybe the entire dorsal stream might be colorblind (not colorblind like red/green colorblindness, but colorblind in the sense of not seeing equiluminant contours, when the two colors defining the contour are equally light). This started a more than year-long argument with David Hubel. His first reaction to my suggesting that the entire dorsal stream might be colorblind was that stereopsis ought to be colorblind, and he thought it wasn't supposed to be (there is, indeed, quite a bit of literature reporting that it is not). So we did the first of dozens of psychophysical experiments designed to test each of David's objections to the idea that dorsal-stream functions are impaired (or disproportionately impaired) at equiluminance. Stereopsis was a difficult test for us because David's equiluminance point was different from mine, so when I thought a stereogram looked flat, he ridiculed me and said that the stereogram had remarkably clear depth, and that maybe I just had defective stereopsis. But then we found a setting where he thought the stereogram went flat, which really surprised him, but was very convincing. So then he said that maybe stereo and motion might be diminished at equiluminance, but what about

illusions of size? What about Vernier acuity? What about the differences in acuity between the dorsal and ventral streams? This went on for a year. I can remember crying when I got home once because I was so frustrated at his stubbornness in refusing to accept this hypothesis, but in the end, we did more than 50 different perceptual experiments, and he ran out of objections, so we published it (Livingstone and Hubel 1987a). Later he claimed that he always thought we had overstated our hypothesis. I regret that he was never completely convinced, but I still think we were right.

Color Constancy

In all this recording from blobs, we rediscovered something else that Charlie Michael had previously reported, namely that these color-selective cells in V1 were strongly surround suppressed, and this surround suppression was color-opponent (Michael 1978). We found that "red" cells respond poorly to a red spot on a red background, but strongly to a red spot on a blue-green background. That is, the color selectivity was dependent on the surrounding wavelengths. Around this time, in the early 1980s, Edwin Land invited us over to his Institute in Cambridge to talk about color. Land was also particularly impressed by how independent one's perception of color can be from wavelength. We usually think of color as being a function of wavelength, but Land had a number of demonstrations that he showed us that revealed how much one's perception of color depends on the surrounding wavelengths, again consistent with what we were seeing physiologically. How dramatic this can be was recently illustrated by a viral photo of a dress that appears to be blue and black to some people and gold and white to others, depending on whether the viewer interprets the dress as being in the shade or in the sun (the cues to this are ambiguous); it is just one of many examples of how strong surround effects can be on color perception. Land had demonstrated that a single wavelength can appear as one color in one context and a completely different color in another. We did an experiment together with Land to test whether this calculation happens in the retina or the cortex. We rigged up a particularly strong surround effect in one visual field that, for normal observers, spreads to influence the color of a spot in the other visual field, across the vertical midline, and tested the effect on a split-brain subject. We did this experiment (and repeated it several times, in this single split-brain individual in one afternoon), and it was quite clear that his color constancy did not cross the vertical midline, indicating that the calculation must depend largely on the cortex, not the retina (since the entire visual field is represented in each retina, but is split down the vertical midline in the two cortical hemispheres). That evening, Land took us to his club (very fancy) where I wrote out a draft of this result (Land et al. 1983) in a lounge, while a woman in a strapless gown played the piano. I remember this quite distinctly because from where I was sitting, she appeared naked.

Interconnected Modular Organization

We had noticed that there was a distinct cytochrome-oxidase pattern in V1 (small round blobs) and a coarser pattern of stripes in V2, and we did years of recording in V1, and later in V2, to try to understand what the pattern meant. Roger Tootell also had been looking at the cytochrome-oxidase patterns, and did gorgeous 2-DG experiments to try to figure it out (most of these papers were written by Roger when he was supposed to be a postdoc in our lab (Tootell, Hamilton, et al. 1988; Tootell, Hamilton, and Switkes 1988; Tootell, Silverman, et al. 1988; Tootell, Switkes, et al. 1988); nevertheless, I hope he agrees that our results have turned out to be marvelously complementary. After recording for a couple of years in V1, we got a windfall when Roger Spealman told us about a large group of about 50 squirrel monkeys out at the primate center who had been bought for a malaria study but hadn't been used (or had been controls for a vaccination). We got them for free, and this allowed us to do a study that otherwise would have been prohibitively expensive: we made a series of HRP injections in V2 to see

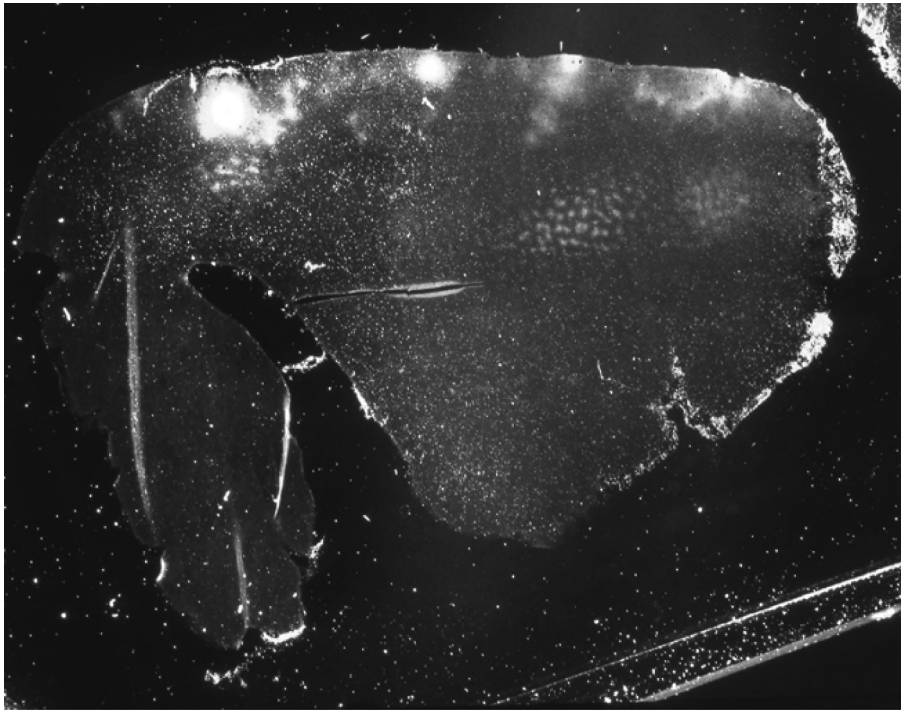

Fig. 1. A section of macaque V1 showing the gorgeous patchy pattern of connections between V1 and V2. This section was a couple of centimeters across, so you could see the patches just by eye; here the patches are made bright by holding the section transversely in the beam of an automobile headlight.

what the anatomical connections were between the two cytochrome-oxidase patterns in V1 and V2. I still have the slides from those experiments: you can see the results just holding up the slide. Figure 1 is an unmagnified picture of one of the slides lit from the side with an automobile headlight (our crude dark-field). They were so clear, and so astonishing! When we injected one kind of stripe in V2, we saw patchy labeling in V1 only in the cytochrome-oxidase blobs; when we injected cytochrome-pale stripes in V2, the labeling in V1 was also patchy, but now only in the interblobs. Thus, blobs in V1 projected to dark stripes in V2, and interblobs in V1 projected to pale stripes in V2; and the feedback connections were also compartment specific (Livingstone and Hubel 1983, 1984a, 1987b). This specificity of interconnectivity was completely unexpected. We also found compartment-selective interconnectivity within V1 and within V2 (Livingstone and Hubel 1984b, 1987b). All this led us to conclude that there were functionally and anatomically distinct pathways carrying different kinds of visual information.

Work/Family

By then I loved science; it never seemed like work. I had a sparse social life, always with other hard-working scientists, and one of those relationships led to my getting pregnant. I decided to have the baby, even though I wasn't married and was up for tenure. No one had gotten tenure in our department since Ed Kravitz, 20 years previously, so I figured I had little chance, especially as my pregnancy became apparent. But the dean, Dan Tosteson, had recently decided that Harvard should abandon the policy of giving professorships only to world-class scientists recruited from outside Harvard, and should start giving tenure to deserving junior faculty who were already at Harvard. Much to my amazement, no one seemed to care that I was pregnant, and they gave me tenure. I juggled the baby, child care, and running a lab. I have no idea now how I did it; I can't even remember much of that time, and I think Steve Macknik mostly ran my lab for a while. I do remember trying very hard not to seem to be abandoning science, so I brought my son, 1 or 2 weeks old, to a faculty meeting. I nursed him there, and mostly the older faculty smiled, and the younger faculty looked anywhere but at me. All the faculty were male. I thought nobody had minded and we were all being very progressive. Years later, when I was talking to a young woman postdoc about how she could handle breastfeeding and working, I told her about breastfeeding at a faculty meeting, and she said "I heard about that." Having a baby was wonderful, fascinating, and satisfying, but doing it with a partner who wasn't ready for it was not so great. I decided to have a second baby alone, and that worked out fine. It was important that I had enough money to have a live-in nanny, though I think at least a third, maybe half, of my salary went to child care or school tuition for many years. It was worth every penny.

Recording all night from anesthetized monkeys was getting exhausting, and my student Steve Macknik convinced me that the future was in recording from alert monkeys. Steve got Richard Andersen, who was then at MIT, to generously show us how to handle and record from alert monkeys. Steve started right off using alert macaques, but David and I decided to try squirrel monkeys first. There is a good reason why hardly anyone does physiology in squirrel monkeys, given that they are neurotic and skittish. We eventually also switched to alert macaques, and I have never gone back. Visual responses in alert monkeys are much more vigorous and clear than in anesthetized monkeys; all you have to do is convince the monkey to keep fixating on a tiny spot. Training monkeys is fascinating. They will do whatever they need to do to get a juice reward, and sometimes what they do is not exactly what you thought you were training them to do. It's like raising children—you need to be aware of what it is you are reinforcing.

There was at the time a debate about whether physiological responses during normal viewing were qualitatively similar to what people had described for decades in anesthetized (paralyzed) animals whose gaze direction was fixed. Jack Gallant (1996) had reported that responses in freely viewing animals were completely different from the kinds of responses that had been described in anesthetized animals (e.g., orientation selectivity). David couldn't believe this was true, so I worked out a way to map receptive fields in freely viewing monkeys using rapidly flashed stimuli and correcting for the monkeys' gaze direction in mapping responses. David and I recorded together from alert monkeys for a while and came to the conclusion that responses in freely viewing animals were indeed qualitatively similar to what had been described previously (Livingstone et al. 1996).

Pushed to Independence

Sadly, I began to realize that even though David and I did science together as equal partners, of course the scientific community didn't see it that way, and David got invitations to talk about our work all over the world, whereas nobody ever invited me anywhere. I realized I would have to branch out on my own, or be his sidekick forever, so I started recording by myself from direction-selective cells. David was never convinced anyway that you could figure out anything about a direction-selective cell using flashed bars. He thought you had to use actual movement. Given that movement on a CRT screen is a series of flashed bars, I don't know why he insisted on this, but he did.

I found that I could map beautifully clear subunits in direction-selective cells using flashed bars, and together with Chris Pack (a postdoc in Rick Born's lab who was much more mathematically competent than I am), we mapped these subunits in two spatial dimensions, plus time (Livingstone et al. 2001). This collaboration was fascinating, and fun, and we could see clearly how direction selectivity, especially in MT, derives from small, simple units, presumably

the V1 inputs, that respond to a particular sequence of two spots of light (or dark). I still suspect that even in V1, direction selectivity will turn out to derive from a spatially offset combination of excitatory and inhibitory inputs. It has been a problem throughout my career that I started college behind in mathematics and never caught up. I wish I had taken statistics at some point.

In the late 1990s two new graduate students started working in my lab: Doris Tsao and Bevil Conway. Doris started studying stereopsis (Tsao et al. 2003), and Bevil followed up David's and my observations on surround opponency in color (Conway 2001), both using my new approach of using rapidly presented stimuli in alert animals and accounting for gaze direction. The monkeys got so good at fixating that the gaze correction wasn't necessary, but it helped early on. Just when Bevil and Doris got well settled in the lab, I was diagnosed with breast cancer. Because Steve, Doris, and Bevil were so independent, I don't think the lab slowed down a bit during my crisis, but my world certainly narrowed down: my two sons and science; nothing else mattered. Happily, surgery was sufficient, and I am an almost 20-year survivor now, but my world never quite widened out again, which is fine by me.

Art

When I gave talks on the differences between the dorsal and ventral visual stream functions, I used images of Op art to illustrate the fact that our motion perception is colorblind, and I discovered that people remembered that part of the talk even if they didn't remember anything else I said. So I started putting more and more works of art in my talk to illustrate various principles of vision. I had come to realize that artists have figured out such things empirically and often create much stronger effects than I could generate from just knowing the underlying science. People liked this so much that after a while I had hardly any science left in my talks. I decided to put all the art stuff I had collected by then into a book, and sent a draft to Abrams Press. The editor Eric Himmel told me he liked the book, but although it was obvious I knew a lot about vision, it was also obvious that I knew nothing about art. He asked me to read an art history book. I got Gombrich's *The Story of Art* and enjoyed it tremendously. But when I got to the Renaissance I was struck by the image of the Mona Lisa. Gombrich urges the reader to look at her and notice: "the amazing degree to which Lisa looks alive. . . . Like a living being she seems to change before our eyes" (Gombrich 1995). He attributes this mysterious effect to Leonardo's technique of *sfumato*, the blurriness of the contours, and thus to the indistinctness, which leaves her emotional state to our imagination. But I noticed that when I looked at her eyes, she seemed to be smiling more than when I looked at her mouth. Her expression wasn't just a function of my mood, but quite clearly a function of my direction of gaze. I realized that this must be due to the differences in acuity between central (high-acuity) and peripheral (low-acuity) vision, so I immediately filtered an image of her face

for low- and high-spatial frequencies, and saw that indeed her smile was more prominent in the low-pass version than in the high. That is, her smile is more apparent to peripheral vision simply because her smile is blurry. And as you move your eyes around the painting her smile systematically enhances and diminishes, depending on where you're looking. I was thrilled by this discovery, and submitted it to half a dozen journals before getting it published as a "Correspondence" in *Science* (Livingstone 2001).

I took my sons to Europe several times when they were young,[3] and toured art museums looking for works of art that showed things that artists had discovered that I could relate to vision science (and training my sons to recognize various artists by their style). In one tiny room in the Louvre, there were four Rembrandt self-portraits, nothing else. In all four of them Rembrandt portrayed himself as having one eye deviating outward. I had been toying with the idea that being stereoblind and having poor depth perception might be an asset for an artist whose goal was to flatten the world onto paper, so when I got back to Boston I collected reproductions of a lot of Rembrandt self-portraits. My student Bevil asked me whether it was always the same eye that deviated outward, and I said, no, if it were I could publish this. Bevil, himself a stereoblind artist, then pointed out that I needed to separate the etchings from the paintings, and when we did, it was clear that it was the eye on the left side of the paintings that always deviated outward, and in the etchings, it was the reverse. I hadn't thought about the fact that when you make an etching, the image is reversed when printed. So Bevil and I quantified the effect, wrote it up, submitted it to a dozen journals, and finally got it published in the *New England Journal of Medicine* (Livingstone and Conway 2004; my only NEJM publication).

Faces

One day Roger Tootell asked me whether I had any trainee who might be interested in doing fMRI (a new and, at the time, somewhat-sketchy technique) in monkeys to try to correlate fMRI with single unit recording. I knew Doris wanted to map stereopsis on a larger scale than the single-unit recording she had been doing, so I asked if she would be interested. She was, and started spending most of her time with Wim Vanduffel and Roger Tootell over at the Martinos Center for Biomedical Imaging, which was at the forefront of fMRI innovation. She succeeded in mapping stereopsis in monkeys using fMRI (Tsao et al. 2003a), and then decided, along with Winrich Freiwald, to see if she could map responses to faces. They revealed a system of face-selective domains in monkey inferotemporal cortex (Tsao

[3] I think it's okay to do things with your kids that also benefit your science. It's certainly efficient.

et al. 2003b), a place where face cells had been frequently found using single-unit physiology, though no large-scale organization had been seen, or even expected, before. Doris and Winrich then wanted to record from these face-selective domains, so they moved back to my lab to work out ways to target their electrode recordings to the fMRI-identified face patches. This was profoundly difficult to do, with roadblocks all along the way (e.g., to move the fMRI-scanned monkeys from the Martinos center to Harvard Medical School took six months of intensive bureaucracy). Doris persisted and, in the end, was rewarded by finding that the fMRI-identified domains were packed full of single units that were spectacularly face selective (Tsao et al. 2006). She and Winrich did a series of brilliant studies on this system of face patches. Doris and Winrich did most of this work on their own; I merely contributed monkeys and lab space, though I did take a large series of photographs of faces of my son's dormitory residents when he was moving in as a high school freshman[4]: each kid, as well as the dorm parents and the custodian, from eight different viewpoints which Doris and Winrich used to study view invariance (Freiwald and Tsao 2010). I enjoy seeing my son's photos in their papers.[5]

When Doris and Winrich found this organization of face patches in monkey inferotemporal cortex, I did a lot of reading about face processing and was surprised to learn how many people in the field of human face perception and human fMRI think that face processing is innate. That is, they assume, with some evidence admittedly, that we evolved specialized domains, with specialized circuitry, for processing this biologically important category of objects. I was surprised by this idea, given the impressive degree of experience (activity) dependence in the development of early sensory areas. I couldn't understand how the wiring of V1 could be completely changed by visual activity, and yet temporal cortex, many synapses further along the hierarchy, could have a genetically predetermined template for something as complex as a face. It seemed more plausible to me that we wire up face selectivity by experiencing faces, especially given that we also have domains selective for text in a nearby part of inferotemporal cortex, and it is unlikely we evolved a domain for text, given how recently in human history literacy has become prevalent.

[4] Both my sons went to boarding school starting in the ninth grade. Where I grew up, only kids with serious behavior problems went to boarding school, but in New England, smart kids often go to boarding school. It is expensive, but it's great because high school is when hormones first kick in and that is a very good time to have someone else set limits.

[5] Somewhere along here, in my late 50s, I married a very nice engineer. I recommend marrying engineers rather than fellow scientists because they are easily movable (they solve rather than contribute to the two-body problem) and are extremely useful. I think programmers and health-care providers might be similarly ideal.

So a new postdoc, Krishna Srihasam, and I trained a group of monkeys to recognize human symbols, in order to find out if monkeys, like humans, could develop a symbol-selective domain as a consequence of intensive early experience. I used my extensive experience with my sons to design what was essentially a video game for teenage boy monkeys. These monkeys did indeed develop symbol-selective domains, but only if they were trained as juveniles, not as adults (Srihasam et al. 2012). This was surprising, but may be similar to human language learning, in that we learn languages easily and fluently as children but not as adults. Along with another postdoc, Justin Vincent, we are now exploring what kind of proto-architecture drives this organization (Srihasam et al. 2014), and I am finally getting to ask the question that has been bugging me ever since Doris and Winrich discovered the face patches: will a baby monkey who has been reared without ever seeing any kind of faces have a normal face-patch system? I spend a lot of time now taking care of baby monkeys while wearing a mask so they never see any faces, and I can't imagine having more fun doing anything else.

On Looking Back

I have succeeded in science beyond my wildest dreams. Ever since I first realized what real science was, as an undergraduate at MIT, I have loved figuring things out about the brain. I have followed my interests, and I feel very lucky to have been able to do so. I do not understand why I could do this and so few other women do. I wish more women would go into science so it would be less lonely, and I think it would improve the culture of science. Although the tenure system does discriminate against women, you don't have to be exceptional to do science; the pervading culture of science is that you do, but I know it's not true.[6] I have gone into a lot of detail so that the meandering, accidental trajectory of my career and the naïve enthusiasm with which I pursued it should be apparent. I hope this will encourage young women to realize that you don't have to know where you're going to make discoveries, though I do think you have to really enjoy it or you won't concentrate and persist, which is critical. I was clueless for a very long time. I still seldom do hypothesis-based research. It usually seems that I am wrestling with questions to which I have no idea what the answer will be. Often, when I do an experiment for which I think I know what the result will be, it comes out completely different. Those are the best.

[6] See Sarah-Jane Leslie et al.'s (2015) interesting article about the inverse correlation between number of women in a field and the perception that you have to be talented or a genius to succeed in the field (think music, math, philosophy): Expectations of brilliance underlie gender distributions across academic disciplines, *Science* 347, 262–265.

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