

Autobiography for 2016 Kavli Prize in Neuroscience
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Gaze at a Josef Albers painting and wonder: how do we see the fantastic interaction of color and form? Albers experimented with the way different shapes and configurations of adjacent color can change visual perception. How does our brain compute these images, leading to perception? My father was trained as a mathematician at the New York University Courant Institute, and then became an aeronautical engineer, designing flying machines and guidance systems for space exploration. My mother was a painter who received an MFA with Philip Guston at the University of Iowa. Both were passionate about what they did, and perhaps because of that passion, I have always had a dual love of science and art. That duality has driven many decisions along my career path.

The USSR launch of Sputnik in 1957 galvanized the United States to upgrade science teaching in public schools, and I was a beneficiary of the terrific hands on high school science courses taught at that time. It is regrettable that our current US public school systems have degraded so much in recent years. I was born in New York City and went to public high school in Connecticut. As a girl, I learned to be curious, to be creative, to take risks and follow the unbeaten path. My father used to take me, along with my brother Jon, skiing – sometimes even on school days just after a huge snowstorm when deep powder was a guarantee. Next day we returned to school with a suntan and a note to the teacher explaining that we had been ill with a very high fever. My brother followed in my father's footsteps, becoming a brilliant engineer and systems analyst until a terrible spinal cord injury a few years ago forced him into early retirement.

Those childhood times together were special. I learned a powerful life lesson: that even at the top of a slope so steep that the bottom was not visible, I could push off, trusting my skill to carry me down the mountain with joy and with safety. My love of skiing and the mountains has permeated my entire life and relationships with husbands, partners and friends. Years ago I became a proficient Telemark skier, venturing into the California and Colorado backcountry for winter camping with my second husband- an accomplished mountaineer. We are divorced (a story for another time), but the memories of those times in the wilderness are as vivid now as they were then. The experience of the utter beauty of nature, as well as the excitement of navigation and exploration into unknown and sometimes dangerous territory, prepared me well for a life of research and discovery. I can understand, and stand in awe of Fridtjof Nansen, the famous Norwegian explorer, who led his team and his ship the Fram on a voyage of discovery in the arctic. Nansen was also neuroscientist and one of the very first to argue in favor of the "Neuron Doctrine". He provided some of the first evidence in 1887 that the nervous system is not a syncytium, but instead composed of individual nerve cells. In the end, after bitter debate, the Neuron Theory proved to be correct: neurons are separate entities, connected to each other by synapses.

I was (and still am) a science nerd, but when I was a child my parents were not worried. (Perhaps they should have been?) For them, it was OK for a girl to be good at science. Most importantly, I learned that science is fun and full of great mysteries and surprises. This fact- the surprise of science- has led me to believe that when an experiment yields exactly the answer that is expected, something special and new may have been missed. Even the best experiments can yield only glimpses of the underlying beauty and complexity of the brain.

In 1965 I began my college undergraduate training at Harvard University (Radcliffe), where I initially declared a major in astrophysics-- an intention dispelled immediately by an exceedingly boring freshman course in astronomy. During my undergraduate years, my formal major was chemistry, but I split course time evenly between science and art. Two courses influenced me profoundly. One, taught by George Wald (who had just won the Nobel prize in physiology or medicine in 1967), was about the chemistry of the visual pigments in the rods and cones of the eye. The other was a class taught by

Rudolf Arnheim, a psychologist with an interest in psychophysics and known for his famous book, "Art and Visual Perception". I enjoyed both classes but was struck by the fact that between the eye at the front end, and visual perception as the output, the brain existed in between only as a black box full of unknown circuits. This realization propelled me directly into the newly born field of neuroscience. In 1968, on the advice of my undergraduate chemistry tutor Frank Westheimer, I reached out to David Hubel and Torsten Wiesel, members of the newly formed (1966) Department of Neurobiology at Harvard Medical School. I spent my senior undergraduate year in a tutorial and lab experience with them, and was enraptured forever by studies of visual system function and development.

In 1969, I graduated from Harvard, receiving a B.A. in Chemistry. Upon graduating, I was honored with a Marshall Scholarship to study for 2 years at University College, London. (Women were not eligible for Rhodes Scholarships in those days.) I received an M.Phil. in Physiology in 1971. The experience at UCL was formative and crucially educational- as a chemistry major at Harvard, I had never taken a single course in biology or physiology. I took laboratory courses in Physiology from Bernard Katz and Paul Fatt, a reading tutorial on the visual system with Semir Zeki, and learned to fabricate glass intracellular electrodes from Bert Sakmann and Bill Betz who were postdocs at the time. My M.Phil. thesis involved searching for long term activity-dependent changes in neuronal spiking, by making intracellular recordings from cerebral cortical neurons with Peter Kirkwood (then in the laboratory of Tom Sears).

It was an exciting time, and living in London was wonderful, but I was anxious to return to the US. The question, though, was how should I continue my career training? Should I apply to medical school or to graduate school? Two of my uncles were clinical neurologists and both urged me to go to medical school. But several years earlier, Sonia- my paternal grandmother- had a devastating stroke. Not enough was known about the brain, and even these two caring physicians could do nothing for Sonia except put her in a wheelchair and consign her to a nursing home. My decision was made: go to graduate school, conduct research and make discoveries.

In 1971 when I returned to Harvard Medical School to begin Ph.D. training with David Hubel and Torsten Wiesel, they were continuing their explorations of function and organization of the visual pathways. Ray Guillery at the University of Wisconsin had just discovered that the connections from retina to LGN in Siamese cats were highly abnormal, with too many ganglion cell axons from each eye crossing in the chiasm and travelling to the wrong side of the brain. (The mechanism of this striking chiasmatic defect, which also happens in humans with Albinism, still remains a mystery of developmental neurogenetics.) A fascinating question generated by this genetic mutation was, how does the rest of the central visual system handle the misrouted axonal projections from the eyes? I discovered that the basic patterning of connections between LGN and visual cortex, and then in turn, between one hemisphere and the other via the corpus callosum, completely rearranges as a consequence of the misrouted retinal inputs! The new patterns of connections, however, preserve topographic rules such that the map of the visual field remains orderly within the cortex. The corpus callosum, in turn, links (new) regions in the two hemispheres that process visual information from the same point in the visual world. These observations of a systematic reorganization of connectivity were among the first to imply a requirement for correlated patterns of activity in refinement of topographic maps in mammalian visual system development.

When I received the Ph.D. in Neurobiology from Harvard Medical School in 1976, I was the first woman to do so. I felt welcomed and appreciated by Hubel and Wiesel, though at the time I expect that they and the Department were conducting their own "experiment" to see if a woman could succeed. Happily the experiment has proved successful. The lab in those years (1971-76) was filled with excitement. From 1973-76, I was also very honored to be appointed as a Harvard Junior Fellow- only the second woman in the then 60-year history of the Harvard Society of Fellows. The discoveries of Hubel and Wiesel of the columnar organization of circuits in primary visual cortex of animals with

binocular vision, which resulted in the Nobel Prize in Physiology or Medicine in 1981, revealed brain circuits of almost crystalline- like perfection. Every day as a student I watched the beauty of visual system organization unfold before my eyes. I thought, “all research must be like this”! Of course, that was not true, but from David and Torsten I learned the joy of research, the importance of articulating and presenting results clearly, and the thrill of going scientifically where few have ventured before. They have both been wonderful mentors then and ever since, and I am forever thankful.

From Hubel and Wiesel's studies of the adult visual system, I began to wonder how the extraordinary precision of adult connections is established during development. It seemed as if the circuits in the adult brain are so precise that they must be hard-wired at the outset, with little left to chance. Or, could visual experience play a role? I remained at Harvard Medical School for postdoctoral training, which was conducted jointly in the laboratory of Dr. Pasko Rakic at Children's Hospital and in the Hubel and Wiesel lab. During that time (1977-78), I learned about the development of the mammalian central nervous system. I realized that brain wiring starts long before birth, and thus acquired training in the elegant techniques of fetal neurosurgery from Rakic. With my co-postdoctoral fellows Simon LeVay and Michael Stryker, we discovered that the system of ocular dominance (OD) columns in cat primary visual cortex only forms gradually from an initially intermixed pattern of right- and left-eye inputs from the LGN relay neurons. This key observation, along with that of Rakic's in the prenatal monkey brain (1976), showed directly that the adult pattern of neural connectivity is not formed initially in the visual cortex, but rather emerges from a less precise, immature pattern. But there was disagreement about how this almost adult pattern can appear before birth. Is there a hardwired blueprint that is not turned on initially and takes time to implement? Or is there an activity-driven process implementing Hebbian synaptic learning rules to refine, prune and remodel synapses according to their use?

This in a nutshell is a question of “nature versus nurture”, and answering it has kept me happily engaged for my entire career as an independent scientist. Because an almost adult pattern of ocular dominance columns in visual cortex forms well before birth in monkeys, and before eye-opening in cats, it was argued, reasonably, that neural activity driven by visual experience could not be a factor. Thus it was assumed that the system had to be hardwired. But there was another alternative: perhaps a special kind of neural activity - generated spontaneously within the central nervous system -could contribute to patterning neural connections, even in utero and before sensory experience.

In 1978 I accepted my first faculty position as an Assistant Professor (and first woman) in Stanford Medical School's Department of Neurobiology; in 1989 I attained the rank of Professor, the first woman in a basic science department at Stanford Medical School to do so. The department Chair, Eric Shooter, created a wonderful place for me to grow and thrive as a young scientist, providing not only intellectual guidance but also, along with his wife Elaine, sustenance. Literally: in the form of home cooked meals (Beef Wellington) over the holidays when I was alone, far away from the east coast and from my family. I learned much from Eric about leadership and mentorship and about the importance of “giving back”: the precious gift of supporting the next generation of neuroscientists. It is fashionable these days to eschew leadership or teaching roles, making the claim that it is “purer” and more important exclusively to conduct research. To me this is an attitude of extreme selfishness. Long after our individual “seminal” discoveries have been built upon and then forgotten, our scientific children, and their children's children will contribute to innovation and knowledge. But this will only happen to the extent that we have created a nurturing and exciting environment and trained our students to conduct high risk, high reward research that wanders away from the beaten track into the land of novel discovery.

When I set up my own lab at Stanford, it occurred to me that by studying the development of connections between the retinal ganglion cells (RGCs: the output neurons of the eye) and their target neurons located in the Lateral Geniculate Nucleus (LGN), it might be possible to address the nature

vs nurture question systematically. These connections are a developmental biologist's dream because they are relatively accessible and highly stereotyped: in adult, retinal ganglion cells from each eye are connected to LGN neurons in separate but adjacent eye-specific layers. However, as with the OD columns in visual cortex, it was assumed that the segregation of RGC axons originating from the right and left eyes into layers within the LGN also had to be hard-wired because the layers form prior to birth and well before the rods and cones function.

In the visual system of binocular mammals from monkey to mouse, this eye-specific segregation of RGCs is not present at the beginning of development. We showed that RGC axons from both eyes are intermixed with each other, and only subsequently do the axons form eye-specific LGN layers, by pruning away sets of wrongly-located synapses and by growing and strengthening correctly located ones. We also found that these early synapses are functional and that the pruning process, which occurs long before vision, requires neural activity. Blocking action potential activity prevented eye-specific segregation. This observation surprised many at first but provided important evidence against the argument that connections are entirely hard-wired. On the other hand, blocking action potential activity did not alter the targeting of RGC axons to the LGN or the initial formation of the retinotopic map, both of which we know now are dependent on hard-wired molecular guidance cues, underscoring the dynamic interplay between "nature and nurture".

The biggest surprise of all came when our lab discovered that the type of neural activity needed for LGN layer formation is generated spontaneously by the RGCs in the form of highly correlated "waves" of firing that sweep across the retina. This discovery happened at Stanford during a wonderful collaboration between Rachel Wong, at the time a postdoc in my lab and now a Professor at University of Washington, and Markus Meister, a postdoc in Denis Baylor's lab and now a professor at Harvard. We used what was then a novel method of multielectrode recording to monitor simultaneously the neural activity of well over 50 retinal ganglion cells and found, incredibly, that even in the dark and prior to vision, neighboring RGCs in the eye fire action potentials synchronously. Subsequently, my lab showed that this synchronous activity is relayed to LGN neurons. It was during this period of research in the 1980' and 1990's that I coined the phrase, "cells that fire together wire together", as well as, "out of synch, lose your link", and began our studies of rules of synaptic plasticity at the retinogeniculate synapse.

At first, some believed that the retinal waves and the need for activity-dependent circuit tuning during early development were "experimental artifacts", and the work was greeted with skepticism. It wasn't an easy time for me or for my students. But nowadays, with the advent of powerful in vivo microscopy, mouse genetics, optogenetics and the ability to observe and to make direct manipulations of neural activity, it is heartwarming to see how these early observations made so long ago have not only gained acceptance but have facilitated marvelous discoveries we never could have imagined. The idea that the eye runs "test patterns" within its circuits to check and correct connections even prior to vision has become more general: this testing process appears to be happening in many other developing brain circuits as well. The idea that there are experience-dependent critical periods during postnatal development has been extended to even earlier times, beginning with endogenous spontaneously generated neural activity during prenatal life.

I have devoted the many years following the discovery of the retinal waves to understanding mechanisms and discovering molecules for how neural activity, propagating through developing circuits, drives synapse pruning and remodeling. To examine how the brain translates neural activity into lasting change in circuits, our lab conducted an unbiased in vivo screen for genes regulated by neural activity in the developing visual system. In other words, we were searching for "nurture" genes. The screen revealed that certain MHC (major histocompatibility) Class I genes are not only expressed in neurons and located at synapses, but are also regulated by neural activity both during development and in the adult. This discovery was entirely unexpected and once again generated great skepticism

because this gene family, famous for its role in the immune system, was not supposed to be expressed by neurons at all, let alone to play a role in activity-dependent synaptic plasticity. In fact, in our initial attempt to publish we were told by the editors to go back to the lab and figure out what we had done wrong! So we went back to the lab, and rather than give up or give in, we have worked to build a stronger case ever since. In a search for MHCI receptors in brain, we found that some neurons express PirB (paired immunoglobulin like receptor B), an innate immune receptor- again unexpected because PirB is not supposed to be present in the healthy brain. Mice lacking PirB have remarkable learning abilities, along with a synapse pruning deficit, and appear to be resistant to the memory loss driven by beta amyloid in mouse models of Alzheimer's disease, potentially opening up entirely new avenues for treatment. It is amazing to me that what began years ago as a purely fundamental neuroscience question about how connections in the developing visual system are tuned up with neural activity and experience has led to discoveries with genuine therapeutic implications for treating cruel diseases such as synapse and memory loss in aging.

In my career, I have been extremely fortunate to teach and work in academic environments where creativity and risk-taking are rewarded. My academic career began at Stanford, but in 1992 I moved to UC Berkeley to be with my husband because Stanford Medical School did not have a position for him. (In those days, retaining women faculty was not a high priority.) Then in 2000 following our divorce, I returned to Harvard Medical School as Chairperson of the very same department where I had trained: Neurobiology. I felt a great honor to be the first woman chair, and also a deep responsibility to give back to the very special faculty and mentors who had given me a chance to become a neuroscientist in the first place. In 2007, I finally returned west, as Director of the Stanford Bio-X program. Bio-X is also part of my "giving back". This university-wide institute funds interdisciplinary, high risk, early stage, training and research with the theme of human health, and it is near and dear to my heart because of my own experience. Knowledge cannot advance without breakthroughs. Genuine breakthroughs that are transformative need resources and most importantly, need someone willing to take the risk. Bio-X takes the risk. While I do not recommend making as many moves as I have made, each one has been exhilarating and has created new environments for ideas and collaborations, facilitating new ways of thinking and tackling research problems not only for me but also for my students.

When I left home in 1965 to go to college, I had no idea what I might become. If you had asked me then to predict my future, I would have said that the one certainty is that I would be married with children. It is incredible to me that my life has turned out so differently. Back then, there were no role models to lead the way. I was married, but waited until too late to have biological children, despite many attempts. Still, there is a silver lining. Over the years, I have been truly privileged to have incredible students and postdocs in the lab; these are my scientific children. Without them, none of the discoveries would have happened. These extraordinary people- many now colleagues and friends- are not only talented and creative, but they have also had the courage to join me on the scientific journey, which has often ventured into unknown and controversial territory. There is no adequate way to express my gratitude to them. The Kavli Prize is especially precious to me because of this recognition for all of us. I give my profound thanks to everyone who has been a part of this journey.