The History of Neuroscience in Autobiography
Volume 11

Edited by Thomas D. Albright and Larry R. Squire
Published by Society for Neuroscience
ISBN: 978-0-916110-03-1

Eric I. Knudsen

pp. 138–176

https://www.doi.org/10.1523/hon.011005

Eric I. Knudsen

Born:

October 7, 1949
Palo Alto, California

Education:

University of California, Santa Barbara, BA (1971)
University of California, Santa Barbara, MA (1972)
University of California, San Diego, PhD (1976)

Appointments:

Assistant Professor, Department of Neurobiology, Stanford
University School of Medicine (1979–1985)
Associate Professor, Department of Neurobiology, Stanford
University School of Medicine (1985–1988)
Professor, Department of Neurobiology, Stanford
University School of Medicine (1988–2016)
Edward C. and Amy H. Sewall Professor, Stanford University School of Medicine (1995–2016)
Chair of Neurobiology, Stanford University School of Medicine (2001–2006)
Professor Emeritus, Department of Neurobiology, Stanford
University School of Medicine (2016–present)

Honors and Awards (Selected):

Newcomb Cleveland Prize, American Association for the Advancement of Science (1978)
Young Investigator Award, Society for Neuroscience (1984)
Troland Research Award, National Academy of Sciences (1988)
American Academy of Arts and Sciences, Fellow (1996)
National Academy of Sciences, Member (2002)
Gruber Prize in Neuroscience, Society for Neuroscience (2005)
Karl Spencer Lashley Award, American Philosophical Society (2008)
American Philosophical Society, Member (2016)

Eric Knudsen has devoted his career to studying how the brain processes information, learns from experience, and selects information for attention. His early research mapped out neural pathways in birds that process auditory spatial information and mediate orienting behavior. A major advance was his discovery with Mark Konishi at Caltech of a topographic map of auditory space in the midbrain of barn owls, a map that results from sophisticated neural computations. Then, with colleagues at Stanford University, he demonstrated how experience during early life shapes the circuits that create this computational map, identified specific sites of adaptive plasticity as well as rules and mechanisms of learning, and discovered methods for increasing plasticity in adult animals. Later, his research shifted to mechanisms that control selective attention. With colleagues at Stanford, he developed behavioral paradigms that quantify the effects of spatial attention in birds and established methods to manipulate signals in the forebrain that modulate sensory information in an attention-like manner. Combining computational approaches with brain slice technologies, he demonstrated how specific brain circuits select information for cognitive decisions, and how other circuits suppress distracting information.

Eric I. Knudsen

Prologue

I have spent my scientific career exploring the mechanisms by which the brain mediates behavior. My love for science began at an early age, and doing science has always been pure pleasure. Throughout my career, I have enjoyed complete freedom to follow my research interests wherever they might lead, and I continue to be amazed that I actually get paid to follow my passion: studying the brain. My interest in the brain applies to the brains of all animals, not just to those of humans. I have found the evolution of the brain to be fascinating as well as uniquely instructive, and I have repeatedly exploited the diversity of species as a tool for discovery.

Over the course of my professional life, my research interests have transitioned from how the brain organizes and processes information, to how it learns from experience, and finally to how it selects information in real-time for attention and decision making. These transitions were stimulating and rejuvenating, as each transition expanded my knowledge in new directions and introduced me to new bodies of literature and communities of scientists. Exploring each of these different aspects of brain function has given me a broad perspective of brain structure, function, and development.

My achievements are a testament to the importance of motivation, focus, and persistence to success in science. In meetings, I am rarely the smartest person in the room. However, I am extremely focused and compulsively organized, and once I have settled on a goal, I am like a bulldog in pursuing it. In this pursuit, I have learned to pay particular attention to findings that deviate from my expectations. Typically, these deviations have arisen from errors in experimental design or data analysis, but sometimes not, and when not, they have led to important advances, if not breakthroughs, in my understanding of a subject. Also, I have learned that nature's solutions to biological problems are almost always simple and logical. When a solution seemed complicated, it was because I did not understand the problem in sufficient detail. When analyzed with sufficient resolution, nature's solutions became intuitively obvious and elegantly simple.

Along with the pursuit of science, working with colleagues and students has been the most inspiring and fulfilling aspect of my professional career. By nature, I am introverted and uncomfortable with public speaking (although I love to talk science in private with anyone!). Early on, I thrived on working alone, and my first 10 publications were single-author publications. Fortunately, I learned as a postdoc the joys and benefits of collaborative research and, as an assistant professor, the rewards of teaching.

These social interactions greatly enriched my life. I have had the privilege of working with brilliant colleagues and teaching some of the brightest and most talented students in the world. These interactions made the scientific quest a fun adventure, and most of what I have achieved scientifically resulted directly from these interactions.

Early Years

I was born in Palo Alto, California, in a hospital just a short walk from my laboratory at Stanford Medical School where I spent nearly my entire career as a neuroscientist. I was a baby boomer, born in 1949 to second-generation Norwegian parents. My father was a New Yorker and had just finished fighting in the Pacific theater in World War II. My mother, also from New York, had interrupted her studies at University of California Los Angeles to marry my father when he returned home from the war. When I was born, they were raising my two-year-old sister, Linda, in a rustic cabin with no running water, in the Santa Cruz Mountains behind Palo Alto, while my father attended the Stanford School of Business. Six years later, we were joined by my second sister, Anne, and after another nine years, by my brother, Karl.

I was raised in the Palo Alto area, except for a few years (ages 9–12) when my family lived in Seal Beach in southern California. Those early years of living at the beach had a major impact on my life. I found that I loved being in and on the ocean, probably an expression of the seafaring genes of my Norwegian ancestors. I spent these formative years walking the sand, fishing, sailing, and body surfing. I was also an avid collector: seashells, rocks, butterflies, whatever. Each collection was organized and the items labeled. Later on, this passion would be expressed as a passion for collecting and organizing scientific data.

When I was 12, my family moved back to Palo Alto, where I completed my high school education. My love of the outdoors and fascination with nature grew. During junior high school, I was heavily involved in the Boy Scouts; both my father and mother were scout leaders, and I became an Eagle Scout. My parents loved the mountains. Family traditions included skiing in the winter and hiking and camping in the summer. I attended summer camps that featured hiking, fishing, and animal husbandry. Meanwhile, my collections continued to grow.

At the beginning of high school, my father quit his job as an office manager and started his own printing business, a profession he had learned from his father. To purchase equipment and rent space for his print shop, we sold our home and rented an old ranch house in the hills behind Palo Alto. The ranch included a barn, pastures, and large apricot and plum orchards. To help cover family expenses, we boarded horses. We also kept chickens and cats (both of which became important later in my scientific studies),

goats, and dogs. I fed the animals, rode the horses, and went everywhere with my dog. As a result of extensive, daily interactions with these various kinds of animals, I learned to appreciate their sophisticated behaviors, as well as their abilities to communicate with each other and with me. I spent countless hours watching and training these animals.

In high school I realized my interest in the natural sciences. In particular, ecology and biology fascinated me. I was mildly dyslexic, and in elementary school, I had received special training in a failed attempt to improve my spelling and reading abilities. Ironically, in high school I found that I enjoyed writing, which proved to be extremely valuable in my research career. I was good at subjects that did not require lots of reading, were logical, and in which the material could be visualized: for example, geometry and physics. I was poor at subjects that required memorization of arbitrary facts or words; I never did learn Spanish despite two tedious years of trying.

While my interests in academics were developing, I also became interested in cars and organized sports. I worked regularly on an old car that I used to drive to school each day. I played water polo and soccer for my high school teams. I also became a scuba diver and an avid surfer, both direct results of my earlier life at Seal Beach. Toward the end of my high school years, surfing became an obsession, and I would drive my old car over the Santa Cruz Mountains to the beach almost every weekend.

To make money, I worked for my father in his print shop. Also, in the middle of summer, I returned to Seal Beach to work as a deckhand on a tuna fishing boat. The boat stayed out for many days at a time, as we followed the schools of Albacore migrating up the southern coast of California.

In 1967, I left home for my undergraduate education at University of California Santa Barbara (UCSB). I chose zoology as my major, and I immersed myself in academics. This was balanced with daily surfing and playing soccer with the university team. During my junior year, I went to study in Goettingen, Germany, as part of the education abroad program. There, I learned to speak German, traveled extensively throughout Europe, and experienced a variety of foreign cultures. This experience dramatically expanded my worldview. My social skills matured, and I became confident.

Awakening to Neuroscience

As a senior at UCSB finishing my undergraduate degree in zoology, I carried out a research project on the daily movement and feeding patterns of limpets in the intertidal zone. I was captivated by this biological research, and I realized that I wanted to become a marine scientist. I also realized that I had no clue how to pursue this goal. So, I went to talk with my academic advisor, Dr. James ("Jim") Case, who was a neuroscientist. Jim encouraged my desire to become a scientist, but he recommended that I try more controlled, laboratory research before committing to marine ecology.

Jim's main focus of research was bioluminescent communication in invertebrates. Along with other exotic marine invertebrates in his laboratory, Jim had an aquarium containing the bioluminescent sea pansy (*Renilla*), a colonial cnidarian that lives in the sand on the ocean floor. He suggested that I study the properties of this animal's bioluminescent signaling. I was immediately struck by the beauty of its behavior: in response to gentle tactile stimulation, *Renilla* produces a wave of brilliant, blue-green light that sweeps across its leaf-shaped surface. The light is triggered by signals traveling in the animal's nervous system, so the bioluminescence displays the properties of neural signaling (all-or-none activation threshold, propagation, refractory period). The traveling waves of light exhibit the same properties as do electrical waves in the developing retina of vertebrates, but the waves can be seen with the naked eye! I spent the spring of my senior year in Jim's lab characterizing how incident light interferes with this bioluminescence.

Because of the enthusiasm with which I tackled this project, Jim invited me to stay on in his lab as a master's student and to join him for a summer of research at the Marine Biological Laboratory at Woods Hole. This was in 1971. It was the exposure to neuroscience at Woods Hole that set me firmly on a path to becoming a neuroscientist. I took the invertebrate zoology course taught by Jim and Alan Gelperin, a professor from Princeton. The course included an independent project. Mine was studying the neural signals that control the rhythmic ventilation (breathing) and swimming movements of horseshoe crabs, which litter the beaches around Woods Hole. This was my first experience with recording neural signals in animals that were involved in generating movements. I watched with rapt fascination as the rhythmic signals recorded from motor neurons, transitioned from patterns for ventilation to swimming and back to ventilation. By listening to these neural signals played through an audiomonitor, I could predict exactly what the animal was about to do! I was hooked.

My research revealed that the neural circuits that generated the rhythmic, oscillatory patterns for ventilation and swimming were located in each of the crab's abdominal ganglia (Knudsen, 1973). This was my first experience with scientific discovery, and I was instantly addicted. For me, nothing compares with the thrill that comes with discovery. These "aha" moments have been unforgettable in my career and have stoked my passion for research.

For my master's thesis, I expanded on this summer project with additional experiments in Jim's lab at UCSB, including cell-tracing studies (neuronal labeling techniques were just being invented) and kinematic measurements. I found that interganglionic connections regulated the strength and timing of the outputs of the ganglionic pattern generators, thereby coordinating the movements of all the crab's appendages (Knudsen, 1975a).

At this time, the field of neuroscience was still in its "wild west" stage. Our understanding of the nervous system was primitive, and the basic tools for conducting research were just being developed (computers had not yet entered the laboratory, and the ability to fabricate various kinds of microelectrodes was an essential skill). Jim supported me, even though my research topic was far outside of his field of interest. Research was driven solely by curiosity, and there was no particular emphasis on studying the human brain or its diseases. Lab members were free to choose their questions, as well as the best species and techniques to answer those questions. This complete freedom to follow my own interests and instincts was exhilarating. I had found my career path.

Graduate Studies with Ted Bullock

While I was completing my master's degree at UCSB, down the California coast at University of California San Diego (UCSD), a Department of Neuroscience had been created through the recent hiring of several international leaders in neuroscience. Dr. Theodore ("Ted") Bullock was one of these leaders. Ted had received worldwide acclaim for his encyclopedic tome (written with Adrian Horridge) that reviewed everything that was known about the nervous systems of invertebrates (*Structure and Function in the Nervous System of Invertebrates*). Jim admired Ted's work, and he recommended that I go to UCSD to pursue my research interests with Ted.

I was accepted into the UCSD Neuroscience Graduate Program in the fall of 1972. I loaded up my red VW bug with my few possessions and drove down to La Jolla (the town where UCSD is located). I had arranged to meet with Ted on that same day, in his office at the Scripps Institution of Oceanography. The walls of his office were lined with aquaria containing all kinds of exotic fish, particularly electric fish (including one huge electric eel). I told Ted about my research at UCSB and showed him a video of the bioluminescent waves of *Renilla*. He became quite excited and animated as we discussed the nervous system and ecology of Cnidarians. Ted invited me to join his lab, and when I returned a few days later, he had already placed my name on the door to one of his student lab rooms. I was in heaven: welcomed into the lab of a brilliant neuroscientist, with my own lab room, located just a short walk from above-average surf.

Although Ted did research on every aspect of brain function (from why sloths are slow, to bat sonar, to the properties of slow wave field potentials in marine rays), when I joined his lab, most of the research projects centered on the recently discovered, electric sense in weakly electric fish (fish that possess electric organs). Because of my early experience with training farm animals, I chose as my first project to train different species of electric fish to report behaviorally when they detected electric fields of different

frequencies and strengths (Knudsen, 1974). I also measured the strength of the electric fields that different species emitted from their electric organs (Knudsen, 1975b). When combined, these measurements enabled me to estimate distances for the electro-detection of objects and for electro-communication among conspecific fish.

I was independent and headstrong, and I valued the feeling of striking out in my own new direction. So, after a year of working with electric fish, I turned my attention to the less-studied, low-frequency electric sense that is possessed by a much wider range of marine species. This sense depends on a special class of electroreceptors that detects standing (direct current) electric fields and is used by fish, sharks, rays, and a few other aquatic vertebrates to locate prey and to navigate in the earth's magnetic field.

For my doctoral thesis, I studied the characteristics of low-frequency electric fields that are analyzed in the catfish midbrain and how the information is represented. Among other things, I found that input from different sensory organs (which together form the acoustico-lateralis system of fishes) is processed in different anatomical subdivisions of the midbrain nucleus (Knudsen, 1978). I also found that the lateral subdivision of this nucleus contains a topographic map of space around the fish (Knudsen, 1976), a finding that was to play a crucial role in my hunt, as a postdoc, for an auditory map of space in owls.

Like Jim at UCSB, Ted gave the people in his lab complete freedom to choose their research projects and experimental species. When it came time to publish, Ted (like Jim) signed on as an author only when he had participated directly in the research (a practice that has been lost in contemporary science). As a result, throughout my years as a graduate student, all of my publications were single-author publications. In hindsight, it would have been good for the historical record to have Jim's and Ted's names on at least some of those papers.

During this period, I met and married my wife, Phyllis, who at the time was working toward a master's degree in fisheries biology. She was to become my lifelong research collaborator and laboratory manager.

Ted's mentoring established the foundation for my career in neuroscience. He created an extraordinarily rich atmosphere of scholarship and research. He attracted to his lab a large number of exceptionally talented postdocs and visiting professors, mostly from foreign countries. His international reputation also brought traveling scholars to visit the lab. He would host special lab meetings, in addition to our weekly meetings, and give everyone a chance to interact with these scholars. Ted had an eidetic memory, was extremely knowledgeable about all aspects of neuroscience, and enjoyed engaging in spirited, scientific debates. Always the gentleman, he would tailor his discussions to match the interests and sophistication of his company, guiding the discussions and making everyone feel involved. Listening to experts engage in debates about current issues in neuroscience

was an effective and entertaining way to learn about science, people, and how to communicate ideas.

Postdoctoral Studies with Mark Konishi

While studying the catfish midbrain, I had observed that the processing of different kinds of information took place in different subdivisions within a structure. I became interested in whether the same principle applies to the central auditory system of terrestrial vertebrates as well. Specifically, my question was: given that the auditory system analyzes sound location and sound identity using fundamentally different kinds of computations, are these respective computations carried out by anatomically segregated, functionally specialized groups of neurons?

A visiting foreign scholar in Ted's lab, Walter Heiligenberg, was a close friend of Masakazu ("Mark") Konishi. Mark had just published spectacular behavioral studies demonstrating the remarkable sound localization capabilities of barn owls. Knowing my interests in studying the processing of stimulus location versus identity in the auditory system, Walter had recommended that I contact Mark about a postdoctoral position in his lab. Fortunately for me, Mark had just moved from Princeton to the California Institute of Technology (Caltech), just up the road from UCSD.

Mark and I met to discuss his research plans at the 1975 Society for Neuroscience meeting (Ted had just finished serving as president of this new society). Mark described to me his intuition that the extreme dependence of barn owls on accurate sound localization for hunting at night would be reflected in an exceptionally high degree of differentiation in their nervous systems for processing auditory spatial information. His plan was to study auditory spatial processing by recording from neurons in the owl's central auditory pathway while presenting sounds from various locations in anechoic space. This approach was relatively novel because the prevailing method for studying auditory space processing was to deliver sounds through earphones and to simulate spatial cues. To enable Mark to pursue a more natural, "free-field" approach, Caltech had built Mark a large ($3 \times 3 \times 5$ m) anechoic room, and a gifted Caltech machinist (who also built Mars landers for NASA) had constructed a speaker-moving system that could position a small speaker at any precisely controlled location, by remote control, on a 1-m-radius sphere centered on the owl's head. With this equipment, we could test the effects of sound source location independently of all other sound properties.

Mark and I were both excited by our discussions at the Society for Neuroscience meeting, and within a few days of returning from the meeting, I had agreed to join his lab as a postdoc to study the processing of auditory spatial information in barn owls. So, after finishing my doctorate with Ted,

Phyllis and I packed up my VW bug and drove to Caltech to begin this new line of research.

To develop protocols for recording from the owl's brain, Mark had teamed-up with John ("Jack") Pettigrew, a faculty colleague who was an expert in cat visual neurophysiology. Before I arrived, Mark and Jack had completed several pioneering studies on information processing in the owl's central visual system and the influence of early visual experience on the development of that system.

The first issue that Mark and I discussed after I arrived was to answer the question: Given the myriad computations that are carried out by the auditory system to analyze sounds, what is the most efficient strategy to identify those computations that are specifically relevant to analyzing stimulus location? We decided to take a "top-down" approach: The idea was to begin by studying how the brain represents space at the highest levels in the auditory pathway. Then, once we understood these high-level representations, we would study specifically how lower-level brain areas process the information used for computing the high-level representation.

We began our top-down attack in the owl's forebrain auditory area called Field L, equivalent to the auditory cortex in mammals. We presented sounds in the free field (rather than through earphones), allowing the owl's external ears to filter sounds naturally, thereby providing all possible spatial cues to the auditory system (the auditory system derives spatial information from frequency-specific differences in the timing and level of sound at the two ears and from the sound's amplitude spectrum, which is shaped by the physical acoustic effects of the head and external ears).

We surveyed the responses of Field L neurons and occasionally encountered neurons that excited us: they could be driven only by sounds originating from a small region of space (receptive field, RF). When we found such a neuron, we spent hours presenting sounds of different kinds (machine-made tones, clicks and noise bursts, and manmade sounds, including rubbing sandpaper, crinkling foil, or snapping fingers) from various locations. Some "space-tuned" forebrain neurons could be driven only by one type of sound, whereas others responded to wide ranges of sound types. Crucially, however, the locations of their RFs remained constant, independent of sound type or level (Knudsen et al., 1977).

Unfortunately, the vast majority of Field L neurons were not of this kind. Typical neurons responded with broad or complex spatial tuning that changed with the spectral properties of the sound. After several months of studying Field L neurons, we became convinced that space analysis was not a primary function of this forebrain auditory area.

In my doctoral research on the acoustico-lateralis system of catfish, I had found that a particular portion of a midbrain nucleus contained a topographic map of the fish's body surface; a map of space (Knudsen, 1978).

The equivalent nucleus in the auditory system of mammals is called the inferior colliucus (IC). Before moving to another forebrain auditory area in the owl, we decided that we should try recording from the IC in the owl's midbrain. I adjusted the trajectory of the electrode to target this structure. On the first attempt, the electrode entered the external nucleus of the inferior colliculus (ICX) and recorded a unit that exhibited the sharpest auditory RF that I had ever seen. This was an unforgettable moment. I ran to get Mark to show him this amazing unit before it was lost. Having spent so long studying neural responses in Field L, it was immediately apparent to both of us that this unit was special: its responses were highly space-specific and it was not selective for sound type or level.

We repeated this experiment numerous times and found that nearly all ICX units were of this special, space-specific type. Following this discovery, additional discoveries came in rapid succession. Most important, we noticed that neighboring ICX units were tuned for nearly the same location and that the locations of the RFs were different in different experiments. Therefore, we prepared for a marathon experiment, in which we would measure RF locations from as many electrode penetrations as possible. The experiment lasted all night and into the next day. In the course of the experiment, it became apparent that RF locations moved systematically from high to low along single electrode penetrations, and from frontal to peripheral as we moved the electrode caudally in the ICX (Knudsen and Konishi, 1978b). Clearly, the ICX represented auditory space as a topographic map. This was another unforgettable moment of discovery. For the final electrode penetration, beginning at about 6 a.m. on the second day, we accurately predicted the RF locations for all three sequential recording sites. We celebrated this moment with bleary-eyed gusto over a late breakfast.

The discovery of an auditory space map was significant because it was a clear demonstration that the brain can create a topographic representation of information that it derives solely through computations (i.e., a computational map). The auditory space map is based on the brain's evaluation and interpretation of interaural time differences (ITD), interaural level differences (ILD), and amplitude spectra. The map demonstrated that the brain arranges neurons topographically within the ICX so that the tuning of neurons to values of ITD, ILD and amplitude spectrum matches the pattern of these cue values as they vary across space for the owl. This discovery led to my first award for science: the Newcomb Cleveland Prize (for "best paper of the year in *Science* magazine"). The letter announcing the award came as a complete surprise, and my elation upon reading it lasted for days.

During the subsequent two years of my postdoc, Mark and I continued to explore the remarkable properties of these space-specific neurons and contrasted them with the properties of auditory neurons in the classical

("tonotopic") pathway in neighboring subdivisions of the inferior colliculus (Knudsen and Konishi, 1978a).

At the same time, my passion for studying animal behavior resurfaced. In my spare time, I hand-raised an owl that had hatched in the laboratory's incubator. This owl ("Dini," short for Houdini because he kept escaping from his cage) became tame and imprinted on me. Occasionally, I would let Dini fly down the long hallways of the Beckman building, over the heads of people eating lunch. His flight was so silent that they rarely noticed this huge (1-meter wingspan) bird passing immediately overhead.

When I was in my office, Dini perched by my desk, and I soon became aware of the distinctive orientation behavior of barn owls: in response to an interesting stimulus, they turn their heads extremely rapidly and accurately toward the stimulus. For them to visually fixate the stimulus, this behavior must be accurate because their eyes are essentially stationary in the head. It occurred to me that we could harness this head-orientation behavior to assess the owl's sound localization capabilities.

A graduate student in Jack's lab (Gary Blasdel) had the idea of measuring the owl's head orientation behavior with a "search coil." At that time, search coils were being used to measure eye movements in monkeys. We attached the coil to the owl's head. We wrapped our own coils, built the required hardware, and Gary wrote the software to calibrate and record head orientation dynamics, and accuracy. We compared orientation accuracy in response to visual versus auditory targets presented in the darkened sound chamber (Knudsen et al., 1979). Differences in visual versus auditory orientation accuracy were ascribed to errors in sound localization. Mark and I tested the effects of different types of sounds, presented from various locations, and compared sound localization behavior with the functional properties of space-specific neurons in the ICX space map (Knudsen and Konishi, 1979).

The three years that I spent with Mark transformed my approach to research. Most important, I learned the advantages and joys of collaborative research. Working with Mark and combining our strengths was fun and efficient. He revealed to me the power of quantitative behavioral studies as a tool for discovery. He also taught me the value of pursuing a dual, behavioral–neurophysiological approach to research: Results from behavioral studies guide physiological experiments toward the measurement of the most functionally important properties of neurons; conversely, the functional properties of neurons predict perceptual capacities and limitations that can be tested behaviorally.

In addition, in Mark's lab I was steeped in neuroethology, the science of natural behavior. While I was studying barn owls, graduate students and other postdocs were studying song learning in songbirds. Mark's office echoed with songs of developing sparrows recorded by microphones set up in their cages. We also went on regular expeditions up the coast of California

to collect songbirds and into the jungles of Trinidad to study echolocating oilbirds (Konishi and Knudsen, 1979). These experiences built on similar experiences I had had in Jim's and Ted's labs, and I became a devout neuroethologist.

Moving to Stanford University

During my third year at Caltech, Denis Baylor visited from Stanford University to give a seminar on photo-transduction in the vertebrate retina. By chance, Mark was away at the time, so I gave Denis a tour of the lab and told him about our experiments. Unbeknownst to me, the Neurobiology Department at Stanford was searching for a new assistant professor. A week after Denis' visit, I received a phone call from Eric Shooter, the chair of neurobiology at Stanford, inviting me to interview for the faculty position. Stanford was already in my blood: Stanford was my father's *alma mater*, and I had grown up roaming its campus and cheering for its football team. I interviewed with the faculty members in this young department (Eric had founded the department just a few years before). Each member was a world-class neuroscientist: Eric Shooter, Denis Baylor, John Nicholls, Jack McMahan, and Carla Shatz. Eric was a Cambridge-trained English gentleman and all of the others had been recruited from Harvard University. As a California beach boy, I was definitely an outlier in this group. Nevertheless, they offered me the position, perhaps as a diversity appointment. For me, the position was ideal, and I accepted enthusiastically.

That summer (1979), Phyllis and I again packed up my VW bug and headed up the California coast to Stanford. This time, I also drove a large rental truck, filled with barn owls that Phyllis, Mark, and I had collected in the hills east of Caltech.

Upon arriving at Stanford, I found that there were no facilities for housing large birds. So, my first priority became building an aviary. I received approval from school authorities to construct an aviary on the roof of our research building. Building the aviary became a departmental bonding experience: the entire faculty followed our progress, and several faculty members, postdocs, and graduate students helped Phyllis and me raise the structure. I quickly learned how close-knit and supportive the Neurobiology Department was: I was not just joining a department, I was joining a family.

Within a few months, my laboratory was ready for action. Phyllis, who had trained as a neurohistologist at Caltech with David van Essen, took over as lab manager and technician. By Christmas, the owls were housed, equipment had been received, and sound chambers had been installed, one of which contained a remotely controlled, speaker-moving system, identical to the one that I had worked with at Caltech.

New Lines of Research Begin at Stanford

The first years at Stanford were golden years. Phyllis and I were the only ones working in the lab. The faculty of the Neurobiology Department, under the leadership of Eric Shooter, created a highly supportive and nurturing environment, which allowed me to thrive. Faculty members attended each other's lectures, hosted dinners in their homes, and shared equipment and secretarial support. Faculty meetings were lively, and decisions were always reached through consensus. Once per year, each faculty member presented a research seminar to the rest of the department, at which recent experiments were discussed, data interpretations were debated, and future experiments were proposed. During the seminar, dinner was prepared and served by another lab group.

Another wonderful aspect of that early time was the process of obtaining grant support: it was simple and efficient. Acquiring funding did not require multiple resubmissions or applications to numerous foundations, as it does today. Upon arriving at Stanford, I wrote one proposal to the National Institutes of Health (NIH) and another to the March of Dimes. These proposals were funded and they paid enough to equip and run my laboratory for five-year periods. Because of the efficiency of the funding process, I was able to concentrate on what I loved doing: research.

Around the time that I moved to Stanford, my research interests began to change from how the brain organizes and processes auditory spatial information to how the brain learns to interpret auditory spatial information correctly based on experience. My new interests were sparked by two observations that I had made as a postdoc at Caltech. First, in attempting to record from neurons in the ICX space map, I would sometimes record instead from the optic tectum (OT), a beautifully laminated structure that surrounds the ICX on its lateral side. When I did, I observed space-specific auditory neurons similar to those in the ICX, but they responded also to visual stimuli. Importantly, the visual and auditory RFs of single OT units were always mutually aligned in space. This was provocative because auditory space tuning depends on the tuning of neurons to sound localization cue values (interaural time and level differences; ITDs and ILDs), whereas visual space tuning depends on topographic connections from the eyes. The question that intrigued me was: How do OT neurons become tuned to exactly the correct values of ITD and ILD so that their auditory and visual RFs mutually align in space? A related question arose from our behavioral study that showed that by plugging one of the owl's ears (monaural occlusion), we could cause the owls to incorrectly localize sounds toward the side of the open ear (Knudsen and Konishi, 1979). The question again was: How does the brain learn the correct relationships between auditory cue values and locations in space so that an animal localizes sounds accurately? The anticipated answer to both of these questions was that the brain learns the

relationships between auditory cue values and stimulus locations based on sensory experience, an expectation that turned out to be correct.

The goal of my first experiments at Stanford was to characterize and quantify the alignment of the auditory and visual space maps in the OT (Knudsen, 1982). The mutual alignment of these space maps would provide me with a metric for the accuracy of the association of auditory spatial cue values with locations in visual space in each animal. To make visual RF measurements, I fabricated a hemispheric visual screen from a 1-meter diameter Plexiglas skylight, which I calibrated to match the speaker coordinates from the speaker-moving apparatus, accurate to $<1°$. Phyllis and I spent many happy days and evenings plotting the auditory and visual RFs of OT units. We made marking lesions to indicate the locations of our recording sites in the OT. Phyllis processed the brains and plotted the RF locations on anatomical reconstructions of the OT. The techniques and results from this study laid the groundwork for our future studies on the role of sensory experience in aligning auditory and visual space maps in the brain.

In parallel with these neurophysiological experiments, we initiated behavioral studies, modeled on the ones I had done at Caltech with Mark, to quantify sound localization accuracy. Here, the challenge was to develop a protocol that would enable us to quantify sound localization accuracy from a single day of measurements, so that we could track changes in accuracy across days following an experimental manipulation. As we were developing this protocol, a graduate student, Steven Esterly, joined the lab.

Steve helped Phyllis with our behavioral experiments, which were yielding exciting results: Consistently, young owls raised with one ear chronically plugged adjusted to the abnormal hearing conditions and learned to localize sounds accurately with the earplug in place (Knudsen et al., 1982). In contrast, adult owls subjected to the same hearing impairment did not. We termed this early plastic period a "sensitive period" (Knudsen et al., 1984a). Interestingly, the ability of owls to recover accurate sound localization following the restoration of normal hearing (removal of the earplug) persisted to a much later age, until after the birds reached sexual maturity. We termed this period a "critical period" in the development of sound localization accuracy (Knudsen et al., 1984b). The developmental regulation of this learning process was similar to that of critical periods for song learning in songbirds, binocular vision in mammals, and language learning in humans (Knudsen, 2004). The neural mechanisms that control these critical periods were not known.

To study neural mechanisms, we needed to find a reliable neural correlate of the learning that we were observing behaviorally. The obvious metric was the mutual alignment of auditory and visual space maps in the OT. Sure enough, when I recorded from the OT of birds that had been raised with a monaural occlusion and still had the earplug in place, auditory

RFs were aligned with visual RFs, indicating that the brain had learned a new mapping of cue values to locations in (visual) space (Knudsen, 1985). Consistent with this conclusion, when the earplug was removed and normal hearing was restored, auditory RFs immediately shifted out of alignment with visual RFs.

The magnitude of this shift in auditory space tuning provided a quantitative measure of the amount of plasticity (learning) that had occurred in the individual owl. Furthermore, auditory RFs gradually realigned with visual RFs over a period of days following earplug removal, at a rate that matched the rate at which birds recovered accurate sound localization behavior. Importantly, these large adaptive shifts of auditory RFs occurred only when owls were monaurally occluded early in life, during the behaviorally defined sensitive period. We realized that we had found an easy-to-measure, reliable neural correlate of sound localization plasticity.

The Hunt for an Instructive Signal

At this stage, I began thinking about the sources of information that the brain might use to guide adaptive adjustments in auditory space analysis. The obvious candidate was vision: although the brain has access to spatial information from other sources, the spatial information provided by the visual system is by far the most reliable and precise. Reinforcing this intuition, we had noticed that in the auditory maps of the ICX and OT, the representation of frontal space was greatly magnified in a way that was not expected from the properties of auditory spatial cue values but that was expected from a retinotopic template of the world (Knudsen, 1982).

To test for an instructive influence of visual input on auditory space processing, Phyllis and I began studying the effects of altering vision (either by blocking vision or by displacing vision with optical prisms) on the adjustment of sound localization behavior. The idea of using displacing prisms originated from Jack Pettigrew (at Caltech), who used light-weight Fresnel prisms to correct for strabismus in his visual experiments on cats. I decided to try these prisms on owls. We built spectacle frames out of welded wire and metal washers, and cemented the frames to the owl's skull.

The initial experimental strategy was to raise owls with one ear occluded. Then, remove the earplug to induce a systematic sound localization error, and measure the effects of blocking vision (black plastic discs inserted into the frames) or displacing vision (matched prisms inserted into the frames) on the recovery of accurate sound localization behavior. The results demonstrated clearly that with vision blocked, sound localization errors remained uncorrected, and that experience with displaced vision caused sound localization to adjust to match the displacement of the visual field caused by the prisms (Knudsen and Knudsen, 1985).

In the next round of experiments, we simply raised owlets wearing displacing prisms, without prior monaural occlusion. Amazingly, these birds adjusted sound localization to match the displacement of the prisms: they learned to orient the head to the side of an auditory target so that they would see the target through the prisms, even though head orientations to auditory targets had initially been accurate (Knudsen and Knudsen, 1989). These results demonstrated the dominant role of vision in calibrating the owl's responses to auditory spatial cues.

While Phyllis, Steve, and I were studying ways to induce adaptive plasticity in owls, John Middlebrooks joined the lab as my first postdoc. His interests were in space coding in the mammalian homologue of the OT, the superior colliculus (SC). He built apparatus to record from cats (the species he had studied as a graduate student), and tested cat SC units with the same free-field sound system that we were using to study owls. He found auditory space tuning and mutual alignment of auditory and visual space maps in the SC, analogous to the properties we were observing in the owl OT (Middlebrooks and Knudsen, 1984, 1987). John's results strengthened the view that multisensory space integration is a salient function of the OT/SC that is shared across vertebrate species.

After six wonderful years at Stanford, my lab was still small. Nevertheless, the progress we had made in understanding the powerful influence of sensory experience in shaping the brain's processing of auditory spatial information had been sufficient for me to be promoted and granted tenure in my department. Meanwhile, as a balance to research and teaching, Phyllis, Steve, and I played volleyball and went scuba diving and sailing, Phyllis and I joined John and his fiancé for dancing, and I reserved early Wednesday mornings for surfing.

The Laboratory Team Grows

In the 1980s, three new lab members, a graduate student (Sascha du Lac), and two postdocs, (Tom Masino and John Olsen) brought fresh ideas, techniques, and energy to the lab, and the culture in the lab was greatly enriched. We now had enough people to begin weekly lab meetings, and the topics of daily discussions ranged widely from acoustics to how the brain plans and executes movements.

New lines of research were initiated, all related to the space map in the midbrain. One line of research was pioneered by Sascha and Tom. They were interested in understanding how the midbrain represents instructions for orientating the head toward attended stimuli and how those instructions are translated into premotor signals in the brainstem. To address these issues, they developed techniques for electrically microstimulating in the brains of owls that were free to move the head.

Microstimulation applied to the owl's OT resulted in a rapid orienting movement of the head. Using this preparation, Sascha demonstrated that the size and direction of the evoked head movements change systematically with the site of stimulation across the OT, revealing a "motor map" of orienting movements, and this motor map is in register with the visual and auditory maps of space (du Lac and Knudsen, 1990). Moreover, by raising owls with vision blocked, she found that the motor map, like the auditory map, is adjusted and calibrated by early visual experience (du Lac and Knudsen, 1991; Knudsen et al., 1991).

Simultaneously, Tom discovered that, like the eye movement commands from the SC in monkeys, the head movement commands from the OT in owls are transformed by the brainstem into the horizontal and vertical components of the desired movement (Masino and Knudsen, 1990). This was surprising because head movements, unlike eye movements, involve many muscle groups with various pulling directions, none of which align with these Cartesian directions. This result indicated, therefore, that the translation of topographic motor commands into horizontal and vertical vector components is a strategy employed by the brain to orient gaze, regardless of the body parts used to accomplish the movements.

During this time, John Olson initiated a line of research that was to become the backbone for future research in my lab. John was interested in exploring how the binaural spatial cues (interaural time and level differences, ITD and ILD) are represented across the OT to create a space map. Answering this question required that we develop techniques for delivering sounds through earphones (to manipulate frequency-specific ITD and ILD cues independently and parametrically). To accomplish this, we pushed the capacities of our computers to synthesize and systematically vary microsecond differences in interaural timing and decibel differences in interaural level. We spent a year searching for the best hardware for delivering sounds directly to the owl's ear canals and writing the software necessary to generate, calibrate, and systematically manipulate the sound. Once these tools were in hand, John found that OT neurons are sharply tuned for both ITD and ILD, that neuronal tuning to ITD and ILD predict their spatial tuning, and that the cue values to which neurons are tuned change systematically across the OT in a pattern that matches the way in which these values change across space for barn owls (Olsen et al., 1989).

The tools that we developed to enable John's research were essential to the next era of research in the lab: exploring the sites and mechanisms of adaptive auditory plasticity in the brain. Previously, our assessment of adaptive changes in the owl's brain relied on measurements that we made using the moveable, free-field speaker. This worked fine for testing neurons that were tuned for space, as in the ICX and OT. However, neurons in the classical auditory pathway that provide input to these structures are tuned,

instead, for sound frequency and are organized in frequency maps ("tonotopic maps"), not in space maps. To identify sites along the auditory pathway where adaptive plasticity occurs, we needed to be able to measure changes in the tuning of neurons to frequency-specific ITDs and ILDs. Thanks to John's project, we now had this capability.

Toward the end of this period, in 1987, I was offered a professorship at University of California San Francisco. The systems neuroscience faculty at UCSF was large, cooperative, and among the best in the world. At Stanford, Carla Shatz and I were the only systems neuroscientists in my department. Although Carla and I greatly enjoyed working and teaching together, the opportunity to team up with the UCSF faculty was attractive. As inducements to keep me at Stanford, my department offered me a promotion and, more important, a commitment to hire another systems neuroscientist to our faculty. At this time, a group of neuroscientists, including Phyllis, Carla, Bill Newsome, and myself, were rooming together at a winter neuroscience conference. By chance, Bill mentioned to Phyllis that he was not content with his job on the east coast. I had known Bill since 1978, when I had been a postdoc and he a graduate student at Caltech. Both Carla and I knew Bill to be a deep thinker and a brilliant scientist. We brought this news back to Stanford and recommended him enthusiastically to our fellow faculty members. Bill came for an interview and was hired. Recruiting Bill to Stanford provided him the resources he needed to realize his full potential as a world leader in neuroscience. Helping to bring Bill to Stanford turned out to be among my most consequential contributions to my department, Stanford University, and the field of neuroscience.

During this period, Phyllis and I adopted our two sons, Chris in 1986 and Keith in 1989. Our expanded family brought us a whole new world of joys, adventures, and challenges, and enriched our lives immensely.

Exploring Mechanisms of Learning

Over the following decade (1990–2000), the lab continued to grow and mature. With increasing lab size came the establishment of new traditions. Early on, Steve had been a scuba diver, sailor, and volleyball player, so Phyllis and I had enjoyed sharing these leisure-time activities with him. As the lab group expanded, communal activities became regular events: volleyball or ultimate Frisbee on Friday afternoons, canoeing the Russian River on summer weekends, skiing in the Sierra Nevada in the winter, and backpacking in the summer. We also enjoyed sailing trips to the Channel Islands (just off the California coast near Santa Barbara). There, we lived off the land, diving for abundant fish, abalone, lobsters, and scallops. Those were the days!

Back in the lab, regular Friday morning lab meetings were instituted for discussing ideas, recent research progress, and publications. We also

established four awards: the "Phineas Gage award" for developing a new lab technique; the "dimpled-brain award" for a major discovery; the "golden owl award" for a paper accepted for publication; and the "biggest brain award" for a graduate student passing the qualifying exam. A perpetual trophy was associated with each award. Every few months, we would go to lunch at a restaurant selected by the winner of the golden owl award, the trophies would be handed out, the winners would explain what they had accomplished, and we would pose for photographs. The winners displayed their trophies proudly (?) by their desks until the next award luncheon. These events contributed to our *esprit de corps*, and they brought me joy.

Our excellent lab morale, although reinforced by social activities, was anchored in the various veins of exciting research that we had begun to mine. We had already established several experimental methods for reliably inducing large, adaptive changes in both sound localization behavior and the functional properties of neurons in the midbrain. Obvious next questions included the following: Where in the brain does the learning take place? What cellular mechanisms underlie the learning? Does the forebrain contribute to the learning?

Michael Brainard, a graduate student, took up the challenge of discovering where in the brain learning takes place. Enabled by our new technology for measuring neural tuning to frequency-specific ITD and ILD, Michael demonstrated that the first site where prism experience alters the brain's representation of binaural cue values is in the ICX, where the midbrain translates auditory cues into a space map (Brainard and Knudsen, 1993). He went on to explore the dynamics of the experience-driven changes in neuronal tuning and the effects of age on these dynamics (Brainard and Knudsen, 1995).

Joachim Mogdans, a postdoc, found that learning in response to experience with monaural occlusion occurs, at least in part, in the classical (tonotopic) auditory pathway, at the site where inputs from the two ears are first compared to measure frequency-specific ILDs (Mogdans and Knudsen, 1994). Thus, his results showed that the site in the brain where plasticity occurs depends on what the brain needs to learn: Experience with monaural occlusion, which changes the values of ITDs and ILDs, causes adjustments at early sites in the pathway where binaural cues are measured. In contrast, experience with displacing prisms—which do not alter the auditory cue values themselves but, instead, change the relationship between normal cue values and locations in visual space—causes adjustments at later sites in the pathway where auditory-visual associations are established.

In 1994, Dan Feldman joined the lab as a graduate student and initiated an exploration of cellular and molecular mechanisms that underlie the adaptive plasticity in the ICX. Dan began by demonstrating anatomically that neurons bringing frequency-specific information to the ICX

acquire new patterns of axonal projections and that the normal and learned projection patterns coexist in the ICX of prism-reared owls (Feldman and Knudsen, 1997). He then developed techniques to manipulate specific types of neurotransmitter receptors with drugs delivered with spatial precision (micro-iontophoresis). This technique enabled him to show that the newly learned responses of ICX neurons are mediated by a special class of neurotransmitter receptors (NMDA receptors) (Feldman and Knudsen, 1998).

While these discoveries were being made in the midbrain pathway, a postdoc, Yale Cohen, explored how the forebrain represents auditory spatial information (Cohen et al., 1998). He joined forces with Tom Masino to identify the forebrain area that controls voluntary changes in gaze direction in owls (analogous to the frontal eye fields in the prefrontal cortex of primates) (Knudsen et al., 1995). Using the same top-down approach that we had used earlier in the midbrain pathway, he studied the representation of auditory spatial information in the forebrain pathway that leads to this area. He found that in the forebrain, neurons are grouped according to their spatial tuning in a patchy representation of space, but they do not form a topographic map of space like the one created in the midbrain (Cohen and Knudsen, 1995, 1999).

Another cohort of superb graduate students and postdocs joined the lab during the latter half of this decade, bringing with them new ideas and interests. To challenge the capacity of the auditory system to make detailed adjustments in its tuning to ITD and ILD, Josh Gold developed an ingenious passive acoustic filter, which he implanted in one of the owl's ears, that altered the timing and level of sound reaching that ear in a frequency-dependent manner. He found that in young owls, experience with this device caused ICX neurons to restore a map of space by adjusting their tuning to ITD and ILD in a frequency-specific manner, so that neurons became tuned to the highly unnatural combinations of cue values that the owls experienced (Gold and Knudsen, 2000a). In addition, he showed that this frequency-specific adaptive tuning results from changes in connectivity within the IC (Gold and Knudsen, 2000b).

Weimin Zheng, a postdoc, investigated molecular mechanisms that underlie prism-induced auditory plasticity. He blocked inhibition in the ICX of prism-reared owls that were expressing a learned space map, thereby unmasking excitatory influences on these neurons. He showed that excitatory connections that support tuning to normal cue values (the original space map) coexist with learned excitatory connections that give rise to the learned space map (Zheng and Knudsen, 1999). After learning, however, responses to the normal connections are suppressed by inhibitory GABAa receptor currents. Thus, in prism-reared owls, the brain uses GABAergic inhibition to select which of the alternative space maps (normal versus learned) is functionally expressed.

Peter Hyde, a graduate student, hunted for the source of the instructive signal that guides the formation of the learned auditory connections in the ICX. He discovered, using anatomical techniques, that a topographic pathway projects back from the OT (which contains a topographic visual map of space) to the ICX (Hyde and Knudsen, 2000). He found that activity in this pathway acts as a template for guiding the formation of auditory connections in the ICX, thereby customizing, for each individual, auditory cue-location associations in the ICX (Hyde and Knudsen, 2002).

Meanwhile, Will DeBello, a postdoc, characterized anatomically the axon remodeling that gives rise to the learned space map in the ICX (DeBello et al., 2001). In addition, he showed that a second site of plasticity exists in the midbrain pathway: in the OT itself. There, experience aligns the auditory space map sent from the ICX with the OT visual space map (DeBello and Knudsen, 2004). Developmentally, this higher-level plasticity continues long after plasticity in the ICX has become severely restricted because of its sensitive period.

While these exciting discoveries were being made in the lab, the neuroscience community at Stanford was expanding dramatically, with excellent neuroscientists being hired into many departments and schools across the university. In addition, Stanford's Neuroscience Graduate Program, which initially was organized and run by the faculty in my department, became more formalized, largely because of the concerted efforts of Howard Schulman.

In my small department, directing the graduate program, running the core course in neuroscience for the medical school, and chairing the department were essential functions that each senior faculty member was expected to perform in turn. I was happy to do my part. So, in 1998, I took over running the Neurosciences Graduate Program from Howard. This was a mixed blessing. On the one hand, I enjoyed interacting with the exceptionally talented students in the Graduate Program, and I was able to have a major influence on their experiences. On the other hand, the responsibilities—including organizing events, implementing policies, arbitrating disputes, and writing training grants—all demanded time. As a result, my time in the laboratory dropped precipitously.

Final Studies on Mechanisms of Learning

As director of the Graduate Program, I benefited greatly from knowing the incoming class and was able to use that knowledge to recruit three stellar students to my lab: Greg Miller, Brie Linkenhoker, and Joseph Bergen. In addition, a bright young postdoc, Yoram Gutfreund, joined the lab.

Greg was interested in searching for evidence of experience-dependent plasticity in the forebrain auditory pathway. He exploited sensory manipulations that we had developed to study plasticity in the midbrain pathway:

early experience either with the acoustic filtering device invented by Josh or with displacing prisms. He found that auditory experience causes adaptive changes in the auditory thalamus of the forebrain pathway, whereas visual experience does not (Miller and Knudsen, 2003). Thus, the site of adaptive plasticity in the forebrain depends on the nature of the sensory disruption, as it does in the midbrain.

Brie was interested in studying adaptive plasticity in the midbrain pathway of adult owls. Contrary to our previous observations, she found that adult prism experience can, indeed, drive large changes in auditory spatial tuning in the ICX. The key is to impose the sensory disruption (prismatic displacements of the visual field) in small, incrementally increasing steps (Linkenhoker and Knudsen, 2002). Even with incremental learning steps, however, the overall changes in adults are smaller than those that are induced in juveniles by a single large disruption, reflecting a capacity for plasticity that appears to be unique to the young, developing brain. Brie also confirmed anatomically that the learned circuitry in the ICX that is formed in response to early prism experience, persists in adulthood even when it has not been used for long periods (after prisms were removed). This preserved learned circuitry can be rapidly reactivated by experience in adulthood, should it become adaptive once again (i.e., when the same prisms are remounted on the owl) (Linkenhoker et al., 2005). This result is reminiscent of the effects of early language learning on language acquisition in adult humans.

Yoram Gutfreund began studying the signals that instruct learning in the ICX. Peter Hyde had demonstrated previously that a topographic, instructive pathway projects from the OT to the ICX. Yoram used pharmacology to open a gate in the OT that allowed for this instructive signal to be transmitted back to the ICX. He did this by blocking inhibition focally in the OT (using iontophoretic application of a GABAa receptor blocker). Opening this inhibitory gate caused space-specific visual signals to appear in the ICX (normally, ICX neurons respond only to auditory stimuli) (Gutfreund et al., 2002). The receptive field location of the gated visual signals in the ICX matched perfectly the auditory spatial tuning at the recording site in the ICX, implying that the gated signals act as a topographic template for shaping auditory spatial tuning. Yoram then showed how this gated visual signal has the properties required for instructing the selection of auditory inputs in the ICX, based on synchronous auditory-visual signals (Gutfreund and Knudsen, 2006).

Joe Bergan was the last member in my lab to study experience dependent plasticity. Inspired by Brie's results indicating that adult owls retain a substantial capacity for adaptive plasticity, Joe tried a new approach to induce plasticity in adults: he exposed owls to strong prisms, which caused large auditory-visual spatial mismatches, but he forced them to hunt and capture live mice to survive. He found that the auditory spatial tuning of

OT neurons shifted significantly further (by a factor of 5) in birds that had to hunt versus in those that were fed in the traditional way, with dead mice (Bergan et al., 2005). The only difference in experience between these two groups of owls was the short time (seconds to minutes) that hunting owls spent each day, tracking and attacking live mice. Although several factors are likely to contribute to this increase in learning, an obvious factor is the heightened attention and arousal of an owl while it attempts to fuse auditory and visual spatial information from a scurrying mouse. The results of Joe's experiments started me thinking about an entirely new topic: how attention might enhance learning and adaptive plasticity in adult owls.

Expanding Horizons and Responsibilities

Over the next decade (2001–2010), my responsibilities to my department, university, and national scientific community continued to grow. In 2001, I stepped down as director of the Neurosciences Graduate Program and took over as chair of my department. Dealing with departmental issues demanded even more of my time. As a result, for the first time in my scientific career, I was not able to carry out experiments. On the negative side, this meant that I no longer experienced the thrill of discovery, and I was not able to test the viability of new lines of research that could be offered to incoming graduate students and postdocs. On the positive side, my absence from the lab freed lab members to try risky experiments themselves and to send the research in my lab in entirely new directions.

Although serving as chair of my department was an enormous distraction from research, it was time well spent. I learned in detail about my department, its staff, students and faculty, budgets and space allocations, and plans for the future of the school and university. My greatest satisfaction as chair derived from overseeing the hiring of new faculty members: we hired one new member every year for four of the five years that I served as chair. In the process, I learned the background, accomplishments, and future goals of each of these superb young scientists, who represented the future of my department. Our practice of having the chair rotate among faculty members contributed greatly to the cooperative atmosphere in the department. Among other things, it gave every faculty member a deep appreciation for the essential work that administrators do to make the pursuit of science and teaching possible for the rest of us, it distributed administrative expertise throughout the faculty, and it increased empathy and tolerance for the challenges faced by the chair.

During this period, I also joined the National Scientific Council on the Developing Child, which turned out to be the most rewarding and enjoyable committee experience of my career. The council was composed of a group of 15 experts in the fields of brain development, child psychology, and economics. It was led by Jack Shonkoff, an expert in children's health

and development, who was passionate about bringing the latest advances in neuroscience and psychology to the benefit of children through changes in public policy. The council was special because we came from different scientific backgrounds and academic cultures, yet we all shared Jack's passion. Twice each year, we gathered at a wonderful location (different each time), where we engaged in intense discussions, lasting several days. We presented to each other our latest research on early brain or child development, we learned from professionals how to communicate our findings effectively to policymakers and to the public, and we planned public seminars and the writing of research and review papers. Our mission was to act strictly as knowledge brokers (we never advocated for any particular public policy): we provided the best scientific knowledge about the effects of early experience on the development of the brain and behavior. By not advocating for specific policies, we maintained our credibility with, and access to, members of all political parties. Through this experience, I became keenly aware of the importance of communicating the implications of the scientific discoveries made in my lab to the general public and, in particular, to policymakers. A review paper that I wrote in collaboration with this council (Knudsen et al., 2006) was the most satisfying to write of all my papers.

Research Focus Changes from Learning to Attention

While I was busy running my department, research interests in my lab began to shift. Ilana Witten, who joined the lab as a graduate student in 2002, introduced computational modeling to our research armamentarium. Whereas I tend to think in pictures and patterns, Ilana analyzed experimental results in mathematical constructs. She applied her mathematical talents to her research: exploring mechanisms that could account for the dynamic properties of the auditory space map. For example, she and Joe Bergan observed dynamic shifts in the locations of auditory RFs in the OT space map in response to moving stimuli (Witten et al., 2006). These RF shifts caused the space map to represent the future location of the moving stimulus, information that is essential for an animal to orient accurately to a moving stimulus despite delays caused by the brain's processing of sensory information and motor planning. Ilana modeled the dynamics of the excitatory and inhibitory influences that result from spatially organized, classical RFs (RFs with excitatory centers and inhibitory surrounds) and showed that these dynamics, which are common to topographic sensory representations in the brain, result in predictive shifts in RF locations. She also modeled the gradual shifts in auditory RF locations that result from sensory experience and demonstrated that a simple learning rule (the "Hebbian rule") can account for the instructive influence of visual inputs (Witten et al., 2008). Her model showed that an instructive input to a network does not need to have specialized anatomical or genetic properties, but instead can exert

its guiding influence through the action of this common learning rule. The mechanistic insights that I gained from Ilana's modeling work convinced me of the importance of including computational modeling as a research tool going forward.

Joe Bergan's experiments, which had revealed substantial space map plasticity in adult owls, started me thinking about "attention" and how attention might increase learning and adaptive plasticity in adults. A postdoc, Dan Winkowski, shared my interest. Dan developed electrical microstimulation techniques that enabled him to explore the influence of descending signals from the forebrain (from a gaze control area called the arcopallial gaze field, AGF) on the representation of sensory information in the midbrain space map. The equivalent area in primates (called the frontal eye field) had just been shown to control spatial attention in monkeys. Dan found that a signal from the AGF (evoked by electrical microstimulation) representing a particular location, does not drive neural responses in the midbrain space map, but it greatly enhances sensory responses to stimuli at that location, and it simultaneously suppresses responses to stimuli at all other locations in the map (Winkowski and Knudsen, 2006, 2007). This effect is reminiscent of Francis Crick's "attentional spotlight." These top-down forebrain effects share many of the properties of top-down effects that have been reported in the visual cortex of monkeys when they attend to a stimulus (Winkowski and Knudsen, 2008). Moreover, with Dan's microstimulation methodology, we were able to manipulate the location and timing of these modulating signals precisely.

Our previous anatomical studies had shown that the AGF projects both to the OT and to a cholinergic nucleus in the midbrain tegmentum called the nucleus isthmi pars parvocellularis (Ipc). The Ipc, which interconnects reciprocally and topographically with the OT and is equivalent to a portion of the parabigeminal nucleus in mammals, had been shown to drive periodic bursts of OT spikes in response to visual stimuli, and it was hypothesized that the Ipc participates in the analysis of visual information. Kristin Maczko, a graduate student, decided to test this hypothesis. Her experiments revealed that Ipc neurons respond to both auditory and visual stimuli from the same location in space (Maczko et al., 2006), a property that is inconsistent with its hypothesized role as a processor of visual information. Instead, the encoding of stimulus location independent of stimulus modality is consistent with a role of the Ipc in regulating sensory responsiveness in a space-specific manner (i.e., acting like an attentional spotlight).

The Ipc is a central component in a midbrain network, found in all vertebrate species, that interconnects extensively with the OT. The unusual patterns of anatomical connectivity within this network suggest that it generates an attentional spotlight like the one proposed by Francis Crick for mediating spatial attention. The promising results from Dan and Kristin's

experiments were consistent with this hypothesis, and they focused my interest on this network.

Finding New Sources of Research Funding

By 2005, the composition and social dynamics of the lab group had changed. Lab members were no longer ocean junkies but, instead, loved the mountains. We enjoyed skiing trips in the winter and backpacking trips in the summer. The traditions of luncheons for the awarding of lab trophies and Friday evening games continued. To maintain balance in my life, I surfed on Wednesday mornings, although a near-drowning experience made me realize that it was time to stop riding big waves. I sailed and backpacked with Phyllis and my two sons in the summer, and I started playing basketball (I am 6' 3") on a weekly basis.

By this time, mechanisms of spatial attention had become the theme of the lab's research. With the transition to studying "attention," a new cohort of students and postdocs began joining the lab all interested in the question of how the brain selects and tags information in real-time for differential processing. This change in research focus was energizing. I immersed myself in the literature on attention research. I found that this field was rich in descriptions of the amazing phenomenology associated with attention, but it had little to say about the neural circuits and mechanisms that actually perform the selection of information or that enhance neural responses representing the selected information. After studying this literature, I wrote my first paper on this topic (Knudsen, 2007) in an attempt to define the various components of attention that needed to be explained mechanistically.

The experiments that excited me now were completely unrelated to the kinds of experiments that we had conducted in the past. It soon became apparent that my long-standing grant support could not be applied to the pursuit of these experiments and that I would need to acquire funding from new NIH study sections and private foundations. This turned out to be a challenge. Over the previous 25 years, I had applied to a single NIH study section and to certain private foundations. They knew my work and had invested in it. I had routinely written each application once, never needing to resubmit. Moreover, the grant reviewers in my previous research field were accustomed to proposals that employed various species as experimental animals to take advantage of evolutionary specializations that facilitated discovery. In contrast, research on attention was dominated by scientists who studied the phenomenology of attention in humans and nonhuman primates. When I applied for funding to study circuit mechanisms of attention in the midbrain of birds, the applications were reviewed by scientists who had little appreciation for, or knowledge of, brain evolution and comparative neuroscience. The dominant opinion was that selective attention was a capacity that could be explored only in the forebrain of primates or, perhaps, rodents. I was disappointed and saddened by this mind-set. To me, it is

obvious that the capacity for selective attention must have evolved early, enabling animals to make adaptive decisions in complex environments, and that the diversity of species offers unique opportunities to learn about the neural mechanisms that mediate this amazing executive capacity.

It took six long years and the publication of 10 papers from my lab to finally convince NIH reviewers of the validity and promise of our novel approach and to award funding for it. Fortunately, my troubles with finding new sources of funding coincided with me stepping down as chair of my department, thereby providing me the time necessary to pursue new funding sources and to do experiments.

Testing the Midbrain Network for a Role in Controlling Attention

An essential capability of a network that controls spatial attention is that it be able to select one from among many competing stimuli for differential processing. In our previous work, we had always presented only a single stimulus at a time to the animal, a highly unusual condition in nature. Now we asked: When multiple stimuli are present simultaneously, how does the midbrain network pick one location to direct an animal's gaze and spatial attention?

Stimulus selection requires a competitive process, a competition to identify the stimulus that is of highest priority at any moment. To study stimulus competition, we needed to invent an experimental protocol that could parametrically manipulate stimulus priority, elicit consistent neural responses across many stimulus repetitions, and quantify the results. Two postdocs, Shreesh Mysore and Ali Asadollahi, took on this challenge. The goal was to find a visual stimulus parameter that, when increased, systematically increased the strength ("salience") of a stimulus, and to which OT neurons did not adapt (responses in the OT typically adapt drastically after just one or a few presentations of a given stimulus). Only then could we make repeated measurements of the effects of stimulus competition.

Shreesh and Ali devoted more than a year to perfecting such an experimental protocol. The solution was to use a looming dot—a dot that grows in size as though it were approaching the animal—as the stimulus. They changed the speed of the loom to manipulate the priority of the stimulus. They found that the strength of OT responses increased systematically with the speed of loom and that OT responses to looming stimuli persisted across many stimulus repetitions. The effectiveness of this stimulus parameter makes sense, given that a looming stimulus predicts an animal's collision with the stimulus, and the speed of the loom correlates with the time to collision.

Shreesh and Ali measured the effects of competition between two stimuli by parametrically varying the relative speeds of simultaneously looming dots while recording the responses of OT neurons that were tuned to the locations of the dots. By applying this stimulus protocol, Shreesh and Ali

observed that the OT space map indicates the stronger of two stimuli, even when the difference between their strengths is extremely small, and represents the "highest priority stimulus" categorically with differentially strong and periodic bursts of spikes (Mysore et al., 2011).

With this competition protocol, we were able to systematically control stimulus selection by the network. Our goal then became understanding the mechanisms that mediate this selection. As mentioned previously, the OT is densely interconnected with several nuclei located in the floor of the midbrain, nuclei that are referred to collectively as the isthmic nuclei. Each of these nuclei receives topographic input from the OT. One of them returns inhibitory (GABAergic) input broadly to the space map. Others return cholinergic input to precisely the location in the OT that provides its input (the Ipc is one of these cholinergic nuclei). Together, these structures form the core of the midbrain selection network (Knudsen, 2011).

Shreesh focused on the GABAergic nucleus, called the nucleus isthmi pars magnocellularis (Imc). The Imc receives topographic input from the OT and sends inhibitory output broadly to the OT. Based on its atypical pattern of interconnections with the OT, previous scientists had hypothesized that the Imc mediates global inhibition across the entire OT space map. Exploiting our competition protocol, Shreesh tested this hypothesis. He combined physiological measurements in the OT with precise, focal inactivation of the Imc, and computational modeling to reveal how this inhibitory circuit mediates stimulus selection (Mysore and Knudsen, 2012). He went on to show that this same inhibitory circuit is critical both to stimulus competition and to forebrain biasing of stimulus competition in selecting the highest priority location (Mysore and Knudsen, 2013, 2014).

At the same time, Ali was studying the role of one of the network's cholinergic nuclei, the Ipc. He combined physiological recordings with focal inactivation of the Ipc to demonstrate that this cholinergic circuit is responsible for both amplifying OT responses to the selected stimulus and causing them to be periodic. Amplified periodic responses in the OT tag a location in the map as the selected location (Asadollahi et al., 2010; Asadollahi and Knudsen, 2016).

Brain Slices: A New Frontier

The results coming from Kristen's, Shreesh's, and Ali's experiments sparked my desire to understand the underlying cellular and molecular mechanisms by which the midbrain network performed competitive stimulus selection. Dissecting molecular mechanisms in a living animal (*in vivo*) is difficult, but it is readily feasible in slices of the brain that are studied in a dish (*in vitro*). However, I had no expertise in, or experience with, brain slice technologies. Moreover, such experiments require several brains per week, far exceeding our supply of barn owls.

Alex Goddard solved these problems. I recruited Alex as a postdoc with expertise in *in vitro* techniques and an interest in understanding cellular mechanisms of network computations. He recognized that domestic chicks are readily available commercially and, like other birds, they possess a highly differentiated midbrain network. He soon discovered that by slicing the chick brain at a specific angle, all of the components of the midbrain network and their anatomical connections could be maintained intact in a single brain slice.

Just as Alex was developing *in vitro* slice techniques using chicks, a graduate student, Devarajan Sridharan ("Sridhar") was characterizing a conspicuous, periodic component of sensory responses (25–50 Hz; called "gamma oscillations") to visual and auditory stimuli in the OT of barn owls (Sridharan et al., 2011). Alex and Sridhar teamed up to study the source and molecular mechanisms of these oscillations in the chick brain slice. They found that oscillations, identical to those evoked by sensory stimuli *in vivo* in owls, were evoked by electrical microstimulation of retinal afferents in chick brain slices. They localized the source of the gamma pattern generator to layer 10 in the OT; they revealed the specific roles of various neurotransmitter receptors in regulating the frequency, amplitude, and persistence of the oscillations; and they showed the contribution of the Ipc cholinergic feedback loop to the amplification of the oscillatory OT activity (Goddard et al., 2012). Astra Bryant, a graduate student, went on to identify the specific type of cholinergic receptor that regulates the amplitude of the response oscillations in the OT (Bryant et al., 2015).

Again exploiting the chick slice preparation, Alex studied details of the inhibitory circuitry in the Imc, circuitry that is essential to competitive stimulus selection by the network. As predicted by Shreesh's computational models, he showed that inhibitory neurons in the Imc mutually inhibit each other on a global scale, causing stimulus selection to operate across all of space and enabling high resolution selection across wide ranges of absolute stimulus strengths (Goddard et al., 2014).

During this final decade of research, the atmosphere in the lab was particularly stimulating. We were exploring the nexus of spatial attention and the midbrain network at multiple levels: molecular, cellular, circuit, network, behavioral, and computational. Discussions in the lab ranged across these levels, and experimental results from one level directly informed experiments at the others. These were exciting times!

The culture in the lab had also changed. Nearly all of the lab members were married, and two of them had children (as did Phyllis and I). Although they all enjoyed the outdoors, several were not experienced in water or mountain sports. Consequently, lab excursions tended toward family activities, such as picking berries and making jam, observing elephant seals on the Pacific coast, ice skating, swim parties, and picnics.

Behavioral Measures of Attention

Together, the results from our *in vivo* experiments on owls, *in vitro* experiments on chick brain slices, and computer modeling studies gave me a satisfying degree of understanding of how the midbrain network selects the highest priority location, and how it amplifies and makes rhythmic the activity associated with that location. The mechanisms we had found were consistent with, and could account for, many of the signature properties of spatial attention reported in primates (Knudsen, 2012). The critical unanswered question was: Do these midbrain circuits actually control spatial attention? The answer to this question required that we study the animal's behavior.

While we had been pursuing physiological and computational studies, Phyllis had worked on developing a behavioral assay to measure spatial attention in barn owls. Among the obstacles that she faced was that each owl had to be hand-raised to be tame enough to be handled and trained. More problematic, she could not find a reward protocol that would induce them to respond to many stimulus presentations reliably every day. Meanwhile, an inexperienced undergraduate student was able to train chickens easily to perform hundreds of sophisticated (delayed match-to-sample) tests reliably in a single test session after just a few weeks of training.

Realizing the necessity for having behavioral assays to measure attention and the many practical advantages of working with chickens over owls, I finally decided to switch all of our experiments to chickens. This was a sad realization because chicks, although cute, do not have the majesty or cachet of owls. Moreover, switching to chickens required a huge effort: a redesign of the laboratory equipment from the ground up. We had to make a new brain atlas for targeting structures; replace our stereotax and recording equipment; and install new behavioral apparatus, including eye-tracking equipment (chickens move their eyes extensively, unlike barn owls). In addition, baseline neurophysiological measurements had to be repeated in chickens. Compounding our challenges, my plan to switch from owls to chickens and from auditory to visual testing was not received well by granting agencies: I had no track record in either domain. Fortunately, Stanford University granted me seed funding, enabling me to embark on this new direction of research.

Once the laboratory was rebuilt to accommodate chickens, two postdocs, Sridhar Devarajan (who had been a graduate student in my lab) and a new postdoc, Jason Schwarz, pushed forward with studies of selective attention in chickens. Being a domesticated species, the chickens were calm and easy to train. More important, they were able to learn difficult tasks, allowing us to measure their performance on tests that were comparable to those used to measure spatial attention in primates. The tasks measured their ability to make perceptual decisions about stimuli (the orientation of small

grids on a computer screen) presented at various locations in space, with and without spatial cueing, and with and without distracting stimuli at other locations. In addition, Sridhar developed a new data analysis framework that allowed us to differentiate between attention-dependent effects on an animal's *sensitivity* to stimuli and changes in the animal's *bias* to respond to stimuli at a particular location (Sridharan et al., 2014a). Using these behavioral tests and this analysis framework, we found that the phenomenology of spatial attention in chickens and primates is remarkably similar (Sridharan et al., 2014b; Sridharan et al., 2017).

Demonstrating a Causal Role of the Midbrain Network in Spatial Attention

We now had a behavioral paradigm that would allow us test for a causal linkage between the midbrain selection network and spatial attention. Our strategy was to make small lesions in the OT or Ipc (the cholinergic feedback circuit), at sites representing a known location, and then test the ability of the animal to attend to that location (to identify the orientation of a small grid at that location). It took several years and the dedication of two tireless technicians, Deepa Ramamurthy and Suzanne van Winden, to help Phyllis train the birds and collect the data on this complicated task. Jason Schwarz placed the lesions in the OT or Ipc of each bird. By the time we were testing the last of these birds, all members of my laboratory, including Sridhar and Jason, had moved on to other positions. For the final year of the project, Phyllis and I worked alone in the lab, as we had when we first arrived at Stanford, 37 years before. Once we had finished collecting and analyzing the data, I concentrated on writing up the results.

Drafting this final research paper was a pleasure. As mentioned previously, I enjoy writing, and the results of this study were clear: a focal lesion in the OT space map rendered birds incapable of deciding the orientation of a visual grid specifically at the lesioned location (Knudsen et al., 2017). This result is critically revealing because the information required by the brain for making decisions about grid orientation is processed in the bird's forebrain visual pathway and not in the midbrain pathway (as is true also in mammals). The experiments demonstrate, therefore, that the OT in chickens, like the superior colliculus (the equivalent structure) in monkeys, controls the routing of forebrain sensory information to networks that make cognitive decisions. That is, it controls selective spatial attention.

This conclusion led me to the realization that the primary function of the OT, throughout evolution, is to act as a "location selection mechanism" for guiding spatial attention and the direction of gaze (Knudsen and Schwarz, 2017). Commanding orienting movements for redirecting gaze, generally considered to be the primary function of the OT, is actually secondary to location selection for attention. That is, the OT is *constantly* directing the

spatial attention of an animal to top priority locations, but it only issues commands for orienting movements to those locations when it is appropriate to do so.

The results also suggest that, across the evolution of vertebrate species, the primary site in the brain where the midbrain network acts to select visual information for attention has changed dramatically. In fish, amphibians and reptiles, the vast majority of visual information passes through the OT on its way to the forebrain, where stimuli are identified. In these species, the midbrain network selects and filters information in the OT itself. In birds, although the pathway through the OT is still the dominant visual pathway, the direct visual pathway to the forebrain (the retino-thalamic pathway) increases in size and importance. In mammals, and especially in primates, the retino-thalamic pathway is the dominant visual pathway to the forebrain. In these later-evolved species, the midbrain's selection of visual information for attention acts more importantly on information that is being conveyed to the forebrain via the direct, retino-thalamic pathway.

Closing the Laboratory

My first thoughts of closing the laboratory arose indirectly from my difficulties in raising funds for the lab. Gradually, my students came to recognize that the entrenched resistance to funding research on "nonstandard" species was a serious obstacle to a successful career. In addition, my lack of reliable long-term funding hampered my ability to recruit new graduate students and postdocs. One day it dawned on me that I would have to make a choice: either change my research back to studies on neural mechanisms of learning in barn owls or close the lab. In 2015, at 65 years of age, I decided it was time to begin closing the lab, a process that proceeded gradually over the next several years.

Upon hearing this news, Dan Feldman, who had been a stellar graduate student in my lab and was now a professor at UC Berkeley, organized a reunion of colleagues who had worked with me during my years at Stanford. He scheduled a symposium, an evening banquet, and a luncheon for the following day. Most of the graduate students, postdocs, and faculty with whom I had worked closely attended. They came from far and wide. It was a wonderful event and, for me, an unforgettable experience.

Once Phyllis and I had finished analyzing the data from our final research project, Phyllis retired, and I continued to write up the results. After submitting this research paper for publication (Knudsen et al., 2017), I began working on a review paper that summarized all that we had learned over the previous 10 years about the circuits and mechanisms that mediate selective attention. This was important because the order in which we had done the experiments was backward to the traditional order: we had analyzed the neural circuits before we had demonstrated the contributions of the circuits to behavior. The review paper enabled me to present our work

as a coherent story from behavior to cellular mechanisms and to place the work in the context of current knowledge about selective attention and how it works (Knudsen, 2018). Publishing this review gave me a sense of completion and closure to my research career. As I write this autobiography, I am an *emeritus* professor, with an office that commands a great view of the Santa Cruz Mountains, and I have free access to Stanford facilities and a permanent A-parking sticker!

Reflections

I was extremely lucky to have lived during a magical era in neuroscience. This era witnessed spectacular advances in our understanding of the brain as well as revolutionary changes in technologies and computational tools. Questions that were only posed as "thought experiments" one year, often became technically feasible just a few years later. Today, experiments are limited more by understanding and imagination than by technology. These are exciting times in neuroscience.

As is true of all careers, my career was profoundly affected by fortuitous events. For example: had Jim Case not been my undergraduate advisor at UCSB, I would have become a marine ecologist, and not a neuroscientist; had Mark Konishi not been a close friend of Walter Heiligenberg, I would not have studied barn owls as a postdoc; had Mark not been away on a trip on the day when Denis Baylor came to give a seminar at Caltech, I would not have been invited to interview for the assistant professorship at Stanford University. I was so lucky that these critical events, and many others, opened up the career path that I followed.

I was also fortunate to have been surrounded throughout my career by extremely bright colleagues and students. One of my greatest joys has been interacting with brilliant, creative people, developing ideas, and discovering scientific truths. It is these interactions and these people who deserve the credit for most of my accomplishments. This also applies to teaching. As mentioned previously, I do not enjoy public speaking. However, team-teaching together with gifted faculty has been extremely rewarding and, at many times, fun.

Lessons Learned

1. Always work on a "big question" that inspires you. Keeping this big question firmly in mind helps to guide your prioritization of experiments and provides you with the motivation necessary to persevere through the periods of tedium and experimental failure that are inherent to the scientific process.
2. Don't be afraid to follow your changing interests. Expect your "big question" to evolve as your career unfolds. By noticing what you enjoy

discussing at the water cooler and how you describe the importance of your research to friends and family, you will realize when your interests are changing. Follow your changing interests.

3. When selecting an experimental animal, consider the advantages afforded by nonstandard species. Millions of years of environmental challenges have selected for the elaboration of amazing behaviors and brain mechanisms in certain species. The elaboration of behaviors and mechanisms makes the exploration of the brain's solutions to a "big question" easier, more informative, and more interesting in these species.
4. Do not be seduced easily by the latest new technologies. Just because new types of measurements can be made does not mean that they provide the best data for answering your question.
5. Maintain a balanced lifestyle. Interleave focused research with other activities that allow your mind to engage the world in completely different ways. Breakthrough ideas often arrive during such periods.
6. Cultivate a rich and diverse set of friends and collaborators. Although many discoveries come through careful thought and introspection, many others result from interactions with people of different backgrounds and points of view. Sharing and debating ideas with colleagues accelerates understanding, increases productivity, and makes science fun.

The Future

There is nothing that compares with the exhilaration that comes with "aha!" moments of scientific discovery: the realization of a truth that no one else, in the history of mankind, has recognized. In retirement, I miss those moments. I also miss the exhilaration of delivering a good seminar or of teaching bright students about new ideas or ways of thinking. However, I do not miss the many administrative duties attendant to being an active faculty member or the stresses of public speaking, especially as my flexibility of thought and reliability of memory decreases.

Although retired, I continue to immerse myself in science. I maintain an office at Stanford, where I read, write, and talk with brilliant people who are shaping the future of neuroscience. I also monitor the growth of my department and follow the progress of the next generation of outstanding faculty members, as they embark on exciting scientific careers.

With substantial unscheduled time at our disposal, Phyllis and I travel often, taking both planned and spur-of-the-moment trips. On a typical weekday, morning office time is followed by workouts in the gym, basketball, pickleball, or oil painting. Wednesday and Sunday mornings I keep open for surfing. Some days are devoted to projects in my community. Occasionally, I go fishing in the ocean for salmon and halibut or fly fishing in the mountains for trout. Finally, and most important, my family continues to be a major

source of joy and happiness, as it evolves and differentiates in the unpredictable ways that families always do. Life is good. *Carpe diem!*

Selected Bibliography

Asadollahi A, Knudsen EI (2016) Spatially precise visual gain control mediated by a cholinergic circuit in the midbrain attention network. *Nat Commun.* 7: 13472.

Asadollahi A, Mysore SP, Knudsen EI (2010) Stimulus-driven competition in a cholinergic midbrain nucleus. *Nat Neurosci.* 13: 889–895.

Bergan JF, Ro P, Ro D, Knudsen EI (2005) Hunting increases adaptive auditory map plasticity in adult barn owls. *J Neurosci.* 25: 9816–20.

Brainard MS, Knudsen EI (1993) Experience-dependent plasticity in the inferior colliculus: a site for visual calibration of the neural representation of auditory space in the barn owl. *J Neurosci.* 13: 4589–608.

Brainard MS, Knudsen EI (1995) Dynamics of visually guided auditory plasticity in the optic tectum of the barn owl. *J Neurophysiol.* 73: 595–614.

Bryant AS, Goddard CA, Huguenard JR, Knudsen EI (2015) Cholinergic control of gamma power in the midbrain spatial attention network. *J Neurosci.* 35: 761–75.

Cohen YE, Knudsen EI (1995) Binaural tuning of auditory units in the forebrain archistriatal gaze fields of the barn owl: local-organization but no space map. *J Neurosci.* 15: 5152–68.

Cohen YE, Knudsen EI (1999) Maps versus clusters: different representations of auditory space in the midbrain and forebrain. *Trends Neurosci.* 22: 128–35.

Cohen YE, Miller GL, Knudsen EI (1998) Forebrain pathway for auditory space processing in the barn owl. *J Neurophysiol.* 79: 891–902.

DeBello WM, Knudsen EI (2004) Multiple sites of adaptive plasticity in the owl's auditory localization pathway. *J Neurosci.* 24: 6853–61.

DeBello WM, Feldman DE, Knudsen EI (2001) Adaptive axonal remodeling in the midbrain auditory space map. *J Neurosci.* 21: 3161–74.

du Lac S, Knudsen EI (1990) Neural maps of head movement vector and speed in the optic tectum of the barn owl. *J Neurophysiol.* 63: 131–46.

du Lac S, Knudsen EI (1991) Early visual deprivation results in a degraded motor map in the optic tectum of barn owls. *Proc Natl Acad Sci USA.* 88: 3426–30.

Feldman DE, Knudsen EI (1997) An anatomical basis for visual calibration of the auditory space map in the barn owl's midbrain. *J Neurosci.* 17: 6820–37.

Feldman DE, Knudsen EI (1998) Pharmacological specialization of learned auditory responses in the inferior colliculus of the barn owl. *J Neurosci.* 18: 3073–87.

Goddard CA, Sridharan D, Huguenard JR, Knudsen EI (2012) Gamma oscillations are generated locally in an attention-related midbrain network. *Neuron.* 73: 567–80.

Goddard CA, Mysore SP, Bryant AS, Huguenard JR, Knudsen EI (2014) Spatially reciprocal inhibition of inhibition within a stimulus selection network in the avian midbrain. *PLoS One.* 9: e85865.

Gold JI, Knudsen EI (2000a) Abnormal auditory experience induces frequency-specific adjustments in unit tuning for binaural localization cues in the optic tectum of juvenile owls. *J Neurosci.* 20: 862–77.

Gold JI, Knudsen EI (2000b) A site of auditory experience-dependent plasticity in the neural representation of auditory space in the barn owl's inferior colliculus. *J Neurosci.* 20: 3469–86.

Gutfreund Y, Knudsen EI (2006) Adaptation in the auditory space map of the barn owl. *J Neurophysiol.* 96: 813–25.

Gutfreund Y, Zheng W, Knudsen EI (2002) Gated visual input to the central auditory system. *Science.* 297: 1556–59.

Hyde PS, Knudsen EI (2000) Topographic projection from the optic tectum to the auditory space map in the inferior colliculus of the barn owl. *J Comp Neurol.* 421: 146–60.

Hyde PS, Knudsen EI (2002) The optic tectum controls visually guided adaptive plasticity in the owl's auditory space map. *Nature.* 415: 73–76.

Knudsen EI (1973) Muscular activity underlying ventilation and swimming in the horseshoe crab, Limulus polyphemus (Linnaeus). *Biol Bull.* 144: 355–67.

Knudsen EI (1974) Behavioral thresholds to electric signals in high-frequency electric fish. *J Comp Neurol.* 91: 333–53.

Knudsen EI (1975a) Centralgenic motoneuron bursts accompanying various gill plate movements in Limulus polyphemus (Linnaeus). *Comp Biochem Physiol A Comp Physiol.* 51: 465–69.

Knudsen EI (1975b) Spatial aspects of electric-fields generated by weakly electric fish. *J Comp Neurol.* 99: 103–18.

Knudsen EI (1976) Midbrain responses to electroreceptive input in catfish—evidence of orientation preferences and somatotopic organization. *J Comp Neurol.* 106: 51–67.

Knudsen EI (1978) Functional organization in electroreceptive midbrain of catfish. *J Comp Neurol.* 41: 350–64.

Knudsen EI (1982) Auditory and visual maps of space in the optic tectum of the owl. *J Neurosci.* 2: 1177–94.

Knudsen EI (1985) Experience alters the spatial tuning of auditory units in the optic tectum during a sensitive period in the barn owl. *J Neurosci.* 5: 3094–109.

Knudsen EI (2004) Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci.* 16: 1412–25.

Knudsen EI (2007) Fundamental components of attention. *Annu Rev Neurosci.* 30: 57–78.

Knudsen EI (2011) Control from below: the role of a midbrain network in spatial attention. *Eur J Neurosci.* 33: 1961–72.

Knudsen EI (2012) Midbrain and forebrain systems for bottom-up control of spatial attention. In: *The Neuroscience of Attention: Attentional Control and Selection* (Mangun GR, ed.), pp. 131–50. New York: Oxford University Press.

Knudsen EI (2018) Neural circuits that mediate selective attention: a comparative perspective. *Trends Neurosci.* 41: 789–805.

Knudsen EI, Konishi M (1978a) Space and frequency are represented separately in auditory midbrain of owl. *J Neurophysiol.* 41: 870–84.

Knudsen EI, Konishi M (1978b) A neural map of auditory space in the owl. *Science.* 200: 795–97.

Knudsen EI, Konishi M (1979) Mechanisms of sound localization in the barn owl (Tyto-Alba). *J. Comp. Physiol* 133: 13–21.

Knudsen EI, Knudsen PF (1985) Vision guides the adjustment of auditory localization in young barn owls. *Science.* 230: 545–48.

Knudsen EI, Knudsen PF (1989) Vision calibrates sound localization in developing barn owls. *J Neurosci.* 9: 3306–13.

Knudsen EI, Schwarz JS (2017) The optic tectum: a structure evolved for stimulus selection. In: *Evolution of the Nervous System, 2nd edition* (Kaas JH, ed.), pp. 387–408. New York: Elsevier.

Knudsen EI, Konishi M, Pettigrew JD (1977) Receptive-fields of auditory neurons in owl. *Science.* 198: 1278–80.

Knudsen EI, Blasdel GG, Konishi M (1979) Sound localization by the barn owl measured with the search coil technique. *J Comp Physiol.* 133: 1–11.

Knudsen EI, Knudsen PF, Esterly SD (1982) Early auditory experience modifies sound localization in barn owls. *Nature.* 295: 238–40.

Knudsen EI, Esterly SD, Knudsen PF (1984a) Monaural occlusion alters sound localization during a sensitive period in the barn owl. *J Neurosci.* 4: 1001–11.

Knudsen EI, Knudsen PF, Esterly SD (1984b) A critical period for the recovery of sound localization accuracy following monaural occlusion in the barn owl. *J Neurosci.* 4: 1012–20.

Knudsen EI, Esterly SD, du Lac S (1991) Stretched and upside-down maps of auditory space in the optic tectum of blind-reared owls; acoustic basis and behavioral correlates. *J Neurosci.* 11: 1727–47.

Knudsen EI, Cohen YE, Masino T (1995) Characterization of a forebrain gaze field in the archistriatum of the barn owl: microstimulation and anatomical connections. *J Neurosci.* 15: 5139–51.

Knudsen EI, Heckman JJ, Cameron JL, Shonkoff JP (2006) Economic, neurobiological, and behavioral perspectives on building America's future workforce. *Proc Natl Acad Sci USA.* 103: 10155–62.

Knudsen EI, Schwarz JS, Knudsen PF, Sridharan D (2017) Space-specific deficits in visual orientation discrimination caused by lesions in the midbrain stimulus selection network. *Curr Biol.* 27: 2053–64, e2055.

Konishi M, Knudsen EI (1979) The oilbird: hearing and echolocation. *Science.* 204: 425–27.

Linkenhoker BA, Knudsen EI (2002) Incremental training increases the plasticity of the auditory space map in adult barn owls. *Nature.* 419: 293–96.

Linkenhoker BA, von der Ohe CG, Knudsen EI (2005) Anatomical traces of juvenile learning in the auditory system of adult barn owls. *Nat Neurosci.* 8: 93–98.

Maczko KA, Knudsen PF, Knudsen EI (2006) Auditory and visual space maps in the cholinergic nucleus isthmi pars parvocellularis of the barn owl. *J Neurosci.* 26: 12799–806.

Masino T, Knudsen EI (1990) Horizontal and vertical components of head movement are controlled by distinct neural circuits in the barn owl. *Nature.* 345: 434–37.

Middlebrooks JC, Knudsen EI (1984) A neural code for auditory space in the cat's superior colliculus. *J Neurosci.* 4: 2621–34.

Middlebrooks JC, Knudsen EI (1987) Changes in external ear position modify the spatial tuning of auditory units in the cat's superior colliculus. *J Neurophysiol.* 57: 672–87.

Miller GL, Knudsen EI (2003) Adaptive plasticity in the auditory thalamus of juvenile barn owls. *J Neurosci.* 23: 1059–65.

Mogdans J, Knudsen EI (1994) Site of auditory plasticity in the brain stem (VLVp) of the owl revealed by early monaural occlusion. *J Neurophysiol.* 72: 2875–91.

Mysore SP, Knudsen EI (2012) Reciprocal inhibition of inhibition: a circuit motif for flexible categorization in stimulus selection. *Neuron.* 73: 193–205.

Mysore SP, Knudsen EI (2013) A shared inhibitory circuit for both exogenous and endogenous control of stimulus selection. *Nat Neurosci.* 16: 473–78.

Mysore SP, Knudsen EI (2014) Descending control of neural bias and selectivity in a spatial attention network: rules and mechanisms. *Neuron.* 84: 214–26.

Olsen JF, Knudsen EI, Esterly SD (1989) Neural maps of interaural time and intensity differences in the optic tectum of the barn owl. *J Neurosci.* 9: 2591–605.

Sridharan D, Boahen K, Knudsen EI (2011) Space coding by gamma oscillations in the barn owl optic tectum. *J Neurophysiol.* 105: 2005–17.

Sridharan D, Steinmetz NA, Moore T, Knudsen EI (2014a) Distinguishing bias from sensitivity effects in multialternative detection tasks. *J Vis.* 14.

Sridharan D, Ramamurthy DL, Schwarz JS, Knudsen EI (2014b) Visuospatial selective attention in chickens. *Proc Natl Acad Sci USA.* 111: E2056–65.

Sridharan D, Steinmetz NA, Moore T, Knudsen EI (2017) Does the superior colliculus control perceptual sensitivity or choice bias during attention? Evidence from a multialternative decision framework. *J Neurosci.* 37: 480–511.

Winkowski DE, Knudsen EI (2006) Top-down gain control of the auditory space map by gaze control circuitry in the barn owl. *Nature.* 439: 336–39.

Winkowski DE, Knudsen EI (2007) Top-down control of multimodal sensitivity in the barn owl optic tectum. *J Neurosci.* 27: 13279–91.

Winkowski DE, Knudsen EI (2008) Distinct mechanisms for top-down control of neural gain and sensitivity in the owl optic tectum. *Neuron.* 60: 698–708.

Witten IB, Bergan JF, Knudsen EI (2006) Dynamic shifts in the owl's auditory space map predict moving sound location. *Nat Neurosci.* 9: 1439–45.

Witten IB, Knudsen EI, Sompolinsky H (2008) A Hebbian learning rule mediates asymmetric plasticity in aligning sensory representations. *J Neurophysiol.* 100: 1067–79.

Zheng GL, Knudsen EI (1999) Functional selection of adaptive auditory space map by GABA-mediated inhibition. *Science.* 284: 962–65.