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David C. Van Essen

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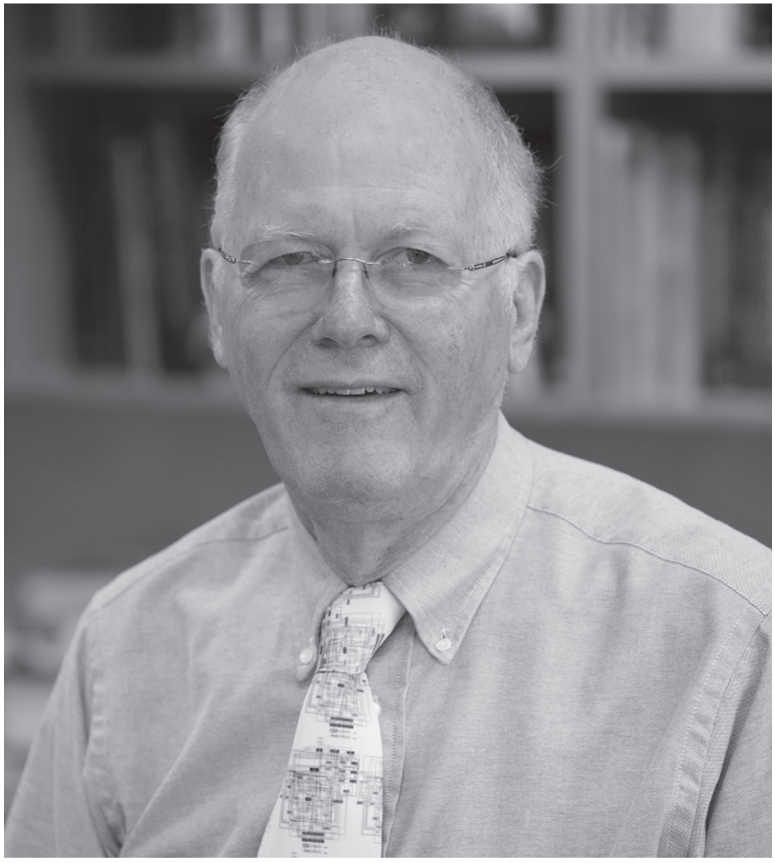

David C. Van Essen

Born:

Glendale, California
September 14, 1945

Education:

California Institute of Technology (honors), Pasadena, CA, Chemistry, B.S. (1967)
Harvard Medical School, Boston, MA, Neurobiology, PhD (1971)

Appointments:

Postdoctoral Fellow, Harvard University (1971)
Postdoctoral Fellow, University of Oslo (1973)
Postdoctoral Fellow, University College London (1975)
Assistant, Associate, Full Professor, California Institute of Technology (1976–1992)
Edison Professor of Neurobiology, Washington University in St. Louis (1992)
Alumni Endowed Professor of Neurobiology, Washington University in St. Louis (2012)

Honors and Awards (Selected):

Helen Hay Whitney Foundation Postdoctoral Fellow, 1973
Alfred P. Sloan Research Fellow, 1978
Best Professor teaching award, California Institute of Technology, 1989
Fellow, American Association for the Advancement of Science, 1994
Distinguished Service Teaching Award, Washington University Medical School, 1992, 2015
Krieg Cortical Discoverer Award (Cajal Club), 2002
Peter Raven Lifetime Achievement Award, St. Louis Academy of Science, 2007
Second Century Award, Washington University School of Medicine, 2015
Editor-in-Chief, *Journal of Neuroscience*, 1994–1998
Founding Chair, Organization for Human Brain Mapping, 1996–1997
Society for Neuroscience Secretary, 2002–2004; President, 2006–2007
President, Association of Medical School Neuroscience Department Chairs, 2006–2008
Senior Editor, eLife, 2015–present

David Van Essen has studied the structure, function, connectivity, and development of cerebral cortex in humans and nonhuman primates. He and his colleagues have developed powerful methods of computerized brain mapping, with a particular emphasis on surface-based visualization and analysis of cerebral cortex. He has been a pioneer in neuroinformatics and data-sharing efforts for nearly two decades. His tension-based theory of morphogenesis accounts for how and why the cortex gets its folds. He has also contributed to our understanding of the functional and hierarchical organization of primate visual cortex. He is a principal investigator for the Human Connectome Project (HCP), an ambitious endeavor to map brain function and connectivity in healthy adults. The HCP is setting new standards for sharing rich and complex neuroimaging datasets with the scientific community.

David C. Van Essen

Preface

It has been my immense good fortune to be engaged in neuroscience research since the late 1960s, when the field was entering a period of explosive progress and growth. My personal neuroscientific journey has taken many twists and turns, by way of somewhat eclectic choices regarding research directions. I have enjoyed the excitement and challenges of delving into a broad spectrum of research arenas, including neuroanatomy, neurophysiology, neural development, computational neuroscience, brain evolution, neuroimaging, and neuroinformatics. My choices of experimental preparation have also spanned quite a range, from leeches and rats to monkeys, humans, and even some great apes. This autobiography aims to weave a coherent narrative, providing context and rationale for how my career evolved in ways that reflect the interactions between long-term visions and various opportunistic decisions. Scientifically, I consider myself first and foremost a cortical cartographer, and the lion's share of this autobiography revolves around efforts to map the structure, function, connectivity, and development of the convoluted cerebral cortex. Counter to my early expectations, I have also devoted a major portion of my professional life to various service and administrative roles. Some of these activities are also woven into the narrative, as they provide a historical as well as personal perspective on how various neuroscience subfields have evolved, particularly in the realms of brain mapping and neuroinformatics.

Four disparate, but interrelated themes are integrated into this essay. One is to provide insights about the origins of important scientific ideas and approaches in which I have been engaged. For example: what are the backstories behind the development of cortical flatmaps, the concept of cortical hierarchies, and the hypothesis of tension-based morphogenesis? How did modern neuroinformatics get off the ground? How was the Human Connectome Project (HCP) conceived and launched? Another is to share vignettes regarding important individuals in my scientific life—mentors, colleagues, and scientific progeny. I have benefited greatly from wonderful mentors and have in turn had the opportunity to train many talented students, postdocs, and technical staff, as well as junior faculty I have helped recruit. Their aggregate accomplishments are truly impressive but can only be told in part. A third aspect entails a hefty dose of personal and family history. My personal adventures are tame in comparison to the often extraordinary and sometimes harrowing adventures told in various

other autobiographies in this series. Nonetheless, family life has always been very important to me—despite the long hours in the lab—and represents a core part of this story. Finally, it has been interesting to reflect on how the future of neuroscience has been seen from various vantage points over the past five decades. Some predictions that I and others have made over the years have borne fruit and proved to be prescient. Many others—arguably the majority—have fallen well short of the mark, some awkwardly or even embarrassingly. Reflecting on the successes as well as failures of past predictions hopefully will provide a bit of entertainment, but might also help improve our batting average in the future.

Childhood

I was born in Glendale, California, in September 1945. My mother, Dorothy Burns, was a direct descendant of the Scottish poet Robert Burns. I'm proud of this lineage, but speculate that the Burns genes for poetic genius became degenerate and contributed to my incorrigible predilection for puns. My father, Roland, was of Dutch lineage, as his father emigrated from Holland and landed at Ellis Island in 1910. Both sides of the family migrated to the Midwest, then eventually to California, and my parents grew up mainly in southern California. For my first six years, we lived in the Los Angeles suburb of Tujunga, but I have only faint recollections of those early days. When I was six, our family moved to Fresno, in the San Joaquin valley, where my father began work as a radio technician, repairing radio equipment for the Highway Patrol and the Forestry Department.

My parents grew up during the Great Depression, and neither had the opportunity to complete a college degree (though my Dad eventually received his B.A. at the age of 50, after many years of night school). They had higher aspirations for their offspring, and they stressed the importance of education to me and my older sister, Carylon. I became hooked on science and technology from an early age, frequently peppering my father with questions about how things worked. I was fascinated by rockets, and when I was about eight, I put pencil to a large sheet of brown shelf paper and drew "detailed" plans for a rocket ship, including a cabin that would comfortably hold my family—grandparents included! This was in 1953—pre-Sputnik days—and my concept of payload capacities was naïve, to put it mildly. Like the rocket itself, my aspirations of becoming a rocket scientist never got off the ground, but my fascination with the space race and its sequelae have never abated.

Around the same time, I got involved in amateur (ham) radio. My father and our close family friend, Jerry Faas, were both hams, and they took me along to "hamfests" where people would show off their "rigs" and talk technical stuff. To get my own license, I learned Morse code, some basic electronics, and rules of the road for amateur radio. I passed my Novice exam

at the tender age of eight and became the youngest ham radio licensee in California. Using a Heathkit radio set that I built, I was on the airwaves, but soon realized that conducting a conversation via Morse code at a paltry five words per minute was painfully slow! Permission to use voice communication required a Technician license, which demanded a deeper understanding of electronics than I could handle at the time.

In 1957, my father was promoted and transferred to the town of Visalia, an hour south of Fresno, where I spent the rest of my childhood. I got along well with my sister Carylon, seeing as how my worst complaint was suffering through Johnny Mathis (her favorite singer, but whose voice I still loathe) crooning while she washed and I dried the dishes. I forgave her later, after my love for classical music began literally while listening to a concert I had been dragged to because she was playing flute in an All-State Orchestra. (Decades later, we are still close.) I was a voracious reader, devouring adventure stories (Huck Finn was a favorite), science fiction (e.g., Isaac Asimov), and other genres. I also spent countless hours poring over our family encyclopedias—initially the *Book of Knowledge*, until my parents sprang for a full 24-volume set of the *Encyclopedia Britannica*. It was a far cry from our modern-day fingertip access to Google and Wikipedia as modes of knowledge exploration, which I don't think were on the radar screen of even the most visionary sci-fi writers back then.

I spent lots of time outdoors, playing with the neighborhood kids, mowing lawns in the neighborhood in order to earn big bucks ($0.25/hour—that's not a typo!), and trying with limited success to broaden the vocabulary of my pet raven (Hercules, or "Herky"). The late 1950s were when the Cold War was near its hottest, and I recall digging a primitive three-foot-deep fallout shelter in our back yard. Highlights of our family activities and adventures included water skiing with our friends the Faases at Millerton Lake outside of Fresno (where my swimming proclivities became permanently spoiled by the warm water temperatures); tent camping in Yosemite before it was completely overrun by tourists; and large family get-togethers at "The Rockies," a sprawling, ramshackle, utterly charming house in the high-desert that was built by my grandfather largely through accretion of scrap materials. My horizons broadened during the summer of 1960 when our family spent six weeks driving around the country, visiting most of the continental United States.

I was generally a well-behaved child, and my mother only occasionally had to put red pepper on my tongue for being sassy. However, I did have a short fuse, and once I lost my temper, it often took many hours before I could cool down and regain emotional balance. Fortunately, I eventually gained better control of my temper, but this occurred gradually, over decades. It makes one wonder whether such changes reflect the imposition of personal "will power," the natural maturation of emotion-related brain circuits, or (most likely) the interaction between the two.

I was raised as a Methodist and was a regular attendee at Sunday school and church. In high school, I became president of our Methodist Youth Fellowship, yet I also began to question the existence of an all-powerful God who could be so tolerant of human suffering and evil. It was increasingly difficult to reconcile with my understanding of how the laws of physics applied to the real world. Our pastor couldn't answer questions to my satisfaction, and I was torn by ambivalence and even guilt about my emerging disbelief in God.

In high school, I did a couple of science fair projects that received honorable mention, but I didn't really gain a sense of what it was like to do scientific research. I loved math and was able to take a fast track when my algebra teacher let me work through a college math book in lieu of regular classwork. In 1961, I spent several weeks at UC Berkeley at a mathematics summer program. This enhanced my passion for math, but also made me realize that I was cut from a different cloth than those who are truly gifted in theoretical mathematics. Even though this was before the free speech movement, Berkeley was a hotbed of liberal and radical thinking. It was my first real exposure to a different political landscape than the very conservative perspective imbued by my parents. It was an eye-opening experience, but it took some years and a transcontinental move before the seeds of liberalism sprouted within my brain.

Caltech Undergraduate Days

In keeping with my passion for science, my first choice for college was Caltech, in Pasadena and near my southern California birthplace. I visited Caltech in 1962 and remember being enthralled by a talk to prospective students given by Richard Feynman, a theoretical physicist and prankster who was already a legend in his time. In the spring of 1963, I was thrilled to receive a letter of admission to Caltech plus a scholarship, which was vital given our family's modest means.

Once at Caltech, I was further inspired by the brilliant, eclectic style of the Feynman physics textbook, so my initial plan was to major in physics. Although I got A grades in freshman physics, I soon decided that theoretical physics, like theoretical mathematics, was not a good fit for what my brain could handle. Instead, I gravitated toward chemistry and lined up a summer job after my freshman year with an organic chemist, Carl Niemann. As fate would have it, that spring Dr. Niemann died suddenly and prematurely of a heart attack. I had no specific interest in biology, but Jerome (Jerry) Vinograd, a wonderful (albeit chain-smoking) molecular biologist, agreed on short notice to take me under his wing. I worked in the Vinograd lab for two summers, using density gradient ultracentrifugation to study supercoiled DNA in bacteriophage and bacteria. I enjoyed this research, but did not find the work fully captivating.

During the second summer—after my sophomore year—I was browsing through the Caltech bookstore and chanced upon *The Machinery of the Brain*, a book by Dean Woolridge. It turned out to be the most transformative book I have ever read. I immediately resolved that I wanted to become a neuroscientist (though that term was not yet in vogue). It was too late to switch my academic major, but starting in my junior year I took all available neuroscience-related courses, including ones taught by Felix Strumwasser (a dynamic and engaging lecturer), Roger Sperry (a great neuroscientist, but regrettably not so inspiring a lecturer), and Max Delbruck (a brilliant physicist turned biophysicist).

As an undergraduate, I was of a studious bent (a nerd, to be blunt) but did manage to enjoy extracurricular activities, including sports. In high school I had never played on an athletic team, opting instead to play trumpet in our marching band. At Caltech, I decided to go out for the freshman basketball team. Caltech was not exactly a powerhouse athletic school—a perennial doormat was more apt, which was hardly surprising given its academic orientation and small student body (180 per class). I joined the Caltech "Beavers" freshman team and found myself on the third string of a team that had only 12 players (go ahead, do the math!). I played only sparingly, usually at the end of games that were hopelessly lost, but I vividly recall what it is to get a hot hand. Our frustrated coach once inserted me early in the game because my teammates were even more hapless than usual. I reeled off several shots that miraculously went in, and ended up scoring a dozen points, which exceeded my aggregate point total for the rest of the season.

In my sophomore year my roommate was John Hosher, who overtly hoped I would improve his own study habits (by osmosis), while on the flip side I was looking for help in cracking my overly nerdy "shell." It worked for both of us, and I hooked up with a great group of friends (guys, because Caltech was not yet co-ed). Extracurricular activities at Tech revolved around the student "houses" (like fraternities but a bit more tame). I became active in inter-house athletic competition and gradually got better in sports such as volleyball and tennis. Intramural athletics also drove home the unpleasant reality of Los Angeles smog during the decade when it was at its worst. Pasadena is snuggled up against the San Gabriel mountains, which are really beautiful—when you can see them. Alas, in those days the noxious smog often completely obscured the nearby mountains. Even worse, the air was foul, and simply breathing deeply while exercising outdoors was painful.

This smoggy storyline segues into an opportunity that enlivened my summer of 1966. Caltech had a Junior Travel Fellowship program in which applicants could propose a self-initiated activity or project anywhere around the world. Motivated by my loathing of smog and inspired by the groundbreaking research of Caltech's Arie Haagen-Smit on the origins and control

of smog, I proposed a low-budget plan to travel around Europe to study pollution control efforts in various northern European countries. On becoming one of several awardees, I used my princely stipend of $1,000 to fly to Europe, buy a bicycle, and hit the road while overnighting in youth hostels. I bought the bike in Denmark ("flatland") and discovered belatedly that my bike didn't have a low enough gear ratio to handle the mountainous roads of Austria and southern Germany. Nonetheless, it was a great experience overall, as I learned a little bit about pollution and a lot more about getting on and around in the world. Biking along various scenic routes provided lots of time to ponder big issues in life. I came to a parting of the ways with religion as a belief system that worked for me. For a while I wondered whether it would suffice to profess being an agnostic, in the sense of not really knowing for sure whether or not God exists. I decided that atheism was a better expression of my core beliefs, in the sense of being willing to bet all of my marbles (including how I would raise children) against his/her existence. To me, the important fundamentals of human morality relate to setting and following high ethical standards, and experience shows that this can be decoupled from religion per se.

Back at Caltech for my senior year, I began research in Felix Strumwasser's lab on a neurophysiology project that involved recording extracellularly from crayfish stretch receptors. My specific topic—how does extracellular potassium affect sensory responses to tail extension?—was less than profound. Nonetheless, the thrill of hearing neuronal spikes crackling away on a loudspeaker resonated deeply with my own neural circuits.

Boston and Harvard Neurobiology

In the fall of 1966, I began looking for graduate schools with training opportunities in neuroscience. Today there is a veritable smorgasbord of outstanding neuroscience graduate training programs to choose among, but the options were very limited back then. I sought advice from Seymour Benzer, who had just arrived at Caltech to begin his pioneering work on *Drosophila* neurogenetics. Seymour encouraged me to check out the Department of Neurobiology at Harvard, which had just been established under the leadership of Stephen Kuffler.

Not long after I submitted my application to Harvard, Dr. Kuffler's secretary called to say that Dr. Kuffler would like to meet me at the LA airport, during a stopover while he was en route to Australia. At that meeting (at a bench in the public area), I found Steve to be gracious and friendly, with a charming Hungarian accent. This and a follow-up interview at Harvard the next month went well, and I was thrilled to join the first class of students admitted to the new department.

Soon after arriving in Boston, I met Jim Hudspeth and Eric Frank, the two other students in the department's inaugural class. Jim, Eric, and

I interacted closely on various fronts over the next few years. One of the most formative was a series of graduate reading courses taught by the five faculty Kuffler had recruited as founding members of the Department of Neurobiology: Ed Furshpan, David Potter, Ed Kravitz, David Hubel, and Torsten Wiesel. Those courses focused on reading classic studies, such as key papers of Hodgkin, Huxley, and Katz. Each weekly session would typically discuss only one or two papers, but we would go over them intensively and exhaustively. It was a great experience in learning how to critically read the literature, probing into what exactly was done, why it was done, and what interpretations and pitfalls to bear in mind. The great strength of these courses was their depth, as they focused on papers that have stood the test of time. The trade-off was that the courses were short on breadth, and I later came to recognize significant gaps in my neuroscience education. Of course, in today's world, the situation is profoundly different in two fundamental ways. The current neuroscience literature contains vastly more publications, and this information can be accessed with blinding rapidity through online resources such as PubMed and Google Scholar rather than trudging to the library and scouring hefty books and journal volumes. But learning how to critically evaluate the literature hasn't become easier and, in some respects, is perhaps even harder to do.

The Harvard Neurobiology Department offered a very collegial as well as stimulating intellectual environment. There was a common room where many of us ate lunch and talked about science, politics, and the like. It also served as a seminar room, in which a parade of outside speakers gave talks that were characterized by frequent interruptions and intense questioning, sometimes to the point that the speaker couldn't get through even half of the planned material. Steve Kuffler was notorious for asking questions that superficially appeared naïve but more often than not keyed on a critically important issue. Faculty, postdocs, and students alike were actively engaged in questions and discussions, making it a great environment for fostering critical scientific thinking.

The number of students, postdocs, and junior faculty in the department grew each year. In the early days, I got to know Nick Spitzer, who was a grad student with Potter and Furshpan before the department had been launched, as well as Zach Hall, John Hildebrand, Paul Patterson, Darwin Berg, and Jack McMahan. Parties at David and Molly Potter's house were highlights, as was the annual departmental Christmas party. The latter included irreverent skits by the grad students and culminated in the infamous Suit Joke told by the inimitable Ed Kravitz. Thanksgiving at the Kuffler house was a memorable occasion for anyone in the department who wasn't able to be with family for the holiday. For many wonderful vignettes focused around Steve Kuffler, I recommend Jack McMahan's book entitled *Steve: Remembrances of Stephen W. Kuffler* (1990) as a great read.

Life with Leeches

During our first year of grad school, Jim, Eric, and I collaborated on a neurophysiology project, working in the Kravitz lab to study identified neurons in lobster abdominal ganglia. This project strengthened my fascination with neurophysiology and my desire to study a "simple" nervous system for my thesis research. Around that time John Nicholls was recruited to the Neurobiology Department from Yale, and by good fortune, his research program meshed well with my interests. John had worked with Steve Kuffler a few years earlier (when Steve was in the Harvard Pharmacology Department), and they had studied the neurophysiology of glial cells in the segmental ganglia of the medicinal leech. At Yale, John continued with the leech nervous system but had decided to focus on sensory neurophysiology rather than glial cells. He and Denis Baylor published a beautiful study (Nicholls and Baylor, 1968) on individually identified sensory neurons, following up on classical neuroanatomical observations by the Swedish neuroanatomist Gustav Retzius (Retzius, 1891). This was right up my alley, and I approached John about joining the lab shortly after his arrival at Harvard. John welcomed me into his group, which initially included Dale Purves and Ann Stuart. My relationship with John was a study in contrasts, insofar as John's effusive highs and lows ("isn't that simply *marvelous*?" or "what a truly *horrid* seminar that was") were counterbalanced by my more laconic and middle-ground style of tending to look at both sides of a given situation. John was a truly dedicated teacher and an excellent speaker and writer, and I gradually learned through his tutelage to improve my style of oral and written communication. John is famous for his wonderful but quirky sense of humor. To get a taste (well, a hefty dose) of it, I recommend his recent book, *Pioneers of Neurobiology: My Brilliant Eccentric Heroes* (Nicholls, 2014).

My thesis research in the Nicholls's lab focused on signaling in primary sensory neurons, particularly a group of three touch-sensitive neurons on each side of each segmental ganglion. Their official names were "T" cells, but in lab parlance they were known (based on size and shape) as "plum" cells to distinguish them from "peach" (P, for pressure) and "pear" (N, for nociceptive) cells. John and Denis had previously reported that leech sensory neurons hyperpolarized dramatically after a burst (tetanus) of impulses, in part due to the activation of an electrogenic sodium pump (Baylor and Nicholls, 1969). I found evidence that this "post-tetanic hyperpolarization" increased sensory thresholds to tactile stimulation of the skin, thereby accounting for some (but not all) aspects of sensory adaptation. In addition, post-tetanic hyperpolarization appeared to contribute to a separate phenomenon, in which action potentials were blocked at branch points and failed to invade the cell body (as they normally did) and in some cases failed to propagate along some but not all axonal branches. This raised the

intriguing possibility that branch point failure might contribute in some systematic way to information processing. A less interesting (but real) possibility was that branch point failure was largely an epiphenomenon, because it generally required stimulation that might lie outside the normal operating range in intact animals. Intermittent branch point failure has been reported in other systems both before and after I published my thesis research, but it does not appear to be a major component or feature in current models of neural information processing. I published my thesis work as a single-author paper—my first scientific publication—in the *Journal of Physiology*. I asked John to be a coauthor, given his major contributions to writing as well as design of experiments, but he refused on grounds that he hadn't actually "done" any of the experiments—a not uncommon practice regarding authorship in those days. My only publication coauthored with John was a *Scientific American* review article on the leech nervous system (Nicholls and Van Essen, 1974).

While carrying out neurophysiological experiments on the leech, I also learned to use the exciting new stick-and-stain method of visualizing neuronal morphology using microelectrodes filled with the fluorescent dye, Procion Yellow. This method had just been developed by Tony Stretton and Ed Kravitz (Stretton and Kravitz, 1968), and it was exciting to see "Golgi-like" visualization of individual, identified sensory neurons through a fluorescence microscope. While the Procion Yellow injections were largely tangential to the main scientific thrust of my thesis, they turned out to be hugely important for the direction my professional career would take. But before proceeding on that front, there are some important facets of nonacademic life to cover.

Life as a Grad Student

Shortly after arriving in Boston in 1967, I responded to a newspaper ad for a room to rent in a third-floor apartment on Francis Street, right next to the medical school. My prospective roommates were three other grad students (two Bobs and a Ted) who offered me a really tiny room, but the price was right: $18/month (again, no typo!). This turned out to be a great living arrangement for the next two years. The congeniality of our living situation was enhanced by our hiring a student from nearby Simmons College to cook dinner for the group on weekdays.

Our dinner conversations were highly animated, more often than not revolving around politics. In 1967–1968, debates about Vietnam were raging around the country, and our dining room was no exception; nor was our departmental lunchroom. As noted already, I had been raised in a very conservative family, both socially and politically. While at Caltech, I had moved past my family's background as teetotalers and had come to enjoy beer and wine, but my political views remained very conservative.

(For context, during the Vietnam era, Caltech was reputed to be the only college in the country whose student body was more conservative than the faculty!) In Boston, many an evening at our Francis Street apartment was devoted to vigorous political discussions. This, along with a lot of reading and introspection, profoundly reshaped my world view. Duly converted to the liberal cause, I drove up to New Hampshire to campaign door-to-door for Eugene McCarthy in the spring of 1968, as he audaciously challenged the sitting president, Lyndon B. Johnson, in the Democratic primaries. McCarthy didn't win the New Hampshire primary, but his strong showing helped reshape the political landscape.

Besides science and politics, there was also time for fun. I played a lot of volleyball and learned to play squash. My roommate Bob Bolender (a grad student in the Anatomy Department) suggested we spend the 1967–1968 Christmas holidays away from the Boston winter. We resolved that Acapulco was an attractive venue in Mexico, but round-trip airfare was outside our budget. Instead, we arranged via a drive-away car company to return someone's car (a gold Cadillac, no less!) from Boston to New Orleans. From there, we took a plane to Mexico City, saw some archaeological sites, then took a bus to Acapulco for a few days of R&R.

Early in the following summer (1968), I took an embryology summer course at Woods Hole, learning a lot about development but doubting at the time that this would loom in my scientific future. For the late summer, Bob had come up with another bright idea for adventure, this time inviting me to join several of his friends on a horsepacking venture in the Cascade mountains east of Seattle. I happily agreed, expecting it to be a lark, but without a glimmer of its long-term implications. One of Bob's friends, Jim Gerlach, lived in the village of Twisp in the foothills of the Cascades. His other two friends in this adventure were Isabel Hunter (a junior in college at UC Riverside) and her mother Margaret, who had driven together up from southern California. During the horsepacking trip (with a lot of rain and with the whole group sharing a single large tent), Isabel and I became good friends, and our relationship soon turned into a transcontinental courtship. As this long-distance romance blossomed, Isabel flew back to see me over Thanksgiving and Christmas holidays. I then flew to California in March of 1969, and we drove Isabel's little Volkswagen Beetle cross-country so we could be together while she finished her undergraduate coursework at Northeastern University. While naturally garrulous, Isabel managed to maintain extended quiet periods, in this instance while I studied for my qualifying exam as we drove along the highways and byways. We were engaged in April 1969, a mere eight months after having met in the Cascades.

When Isabel and I considered when and where to hold our wedding, we benefited from another fortuitous turn of events. It turned out that Steve Kuffler was planning to spend the summer at the Salk Institute in La Jolla, California, where he was a nonresident fellow. Steve invited John Nicholls

to join him so they could collaborate on experiments and also work on a soon-to-be-famous textbook, *From Neuron to Brain* (1976). Steve and John in turn invited several colleagues, including me, to join this venture (which included trucking several full neurophysiology rigs transcontinentally for the summer). The summer was productive scientifically and also afforded a great opportunity to become better acquainted with these colleagues as well as others at the Salk Institute. On the personal front, it conveniently enabled Isabel and me to plan for a July wedding in Isabel's home town of Fallbrook, not far from La Jolla. John and Steve attended the wedding—the first (and almost the only) time I saw John wearing a tie. The wedding was fun, and Isabel recalls that I was rather more nervous about an informal research presentation I was giving at the Salk the week before than about reciting my wedding vows. Isabel is as outgoing as I am reserved, and she embodies the adage of "A stranger is a friend she hasn't yet met." We recently celebrated our 46th anniversary, with two fine sons and four grandchildren as delightful progeny.

Drafty Days in Boston

In the fall of 1969, Isabel and I settled into a small apartment in Allston, between Boston and Cambridge. Isabel got a job at the Peter Bent Brigham Hospital, tissue typing for kidney transplants in the early days when there were no computers and blood draws were done without using gloves. One night in early December, we were awakened by a call from Mike Biglow, a close high school friend. Mike said, "Hi, David. Isn't your birthday September 14th?" When I replied "Yes, but so what?" he responded, "Well, congratulations may not be in order, but you should know that you are *number one* in the draft lottery!" That was indeed the case, and my angst about it heightened soon thereafter when the Selective Service canceled my student deferment. Some months later, I passed my Army physical exam and being drafted into the Army was an imminent prospect.

My options were limited and not attractive. Option 1 was to let myself be drafted, which would entail serving for two years in the Army with a high probability of being sent to Vietnam. Option 2 was to promptly volunteer for the Navy or Air Force, which would entail serving for an additional year in exchange for a higher probability of avoiding the front-line infantry. Option 3 was to seek political asylum in Canada, which quite a few young men were electing to do around that time, but which would have entailed profound career and personal implications. Option 4 was to wangle a way into medical school, where student deferments were still possible. Jim Hudspeth managed to go this route, but that didn't work out for me.

While pondering these options, Option 5 emerged through the intervention of Lady Luck. On a visit to Isabel's brother's house in Rhode Island one fine summer weekend in 1970, I played a pick-up game of touch football with

a group that included Isabel's beefy brothers. I discovered after the game that I had somehow "blown a gasket" in the sense of having a recurrence of an inguinal hernia that had been surgically repaired a decade earlier. My initial consternation ("Oh, no, not this added to my other woes!") quickly turned to immense relief upon realizing that I could not be forced to have elective surgery before being officially drafted. Thus, while the injury was "below the belt," my escape from being drafted was completely above board. I was now damaged goods, and my draft status was converted to an ineligible 2F status that allowed me to stay out of the Army. For the next three years, Isabel and I lived in a fourth-floor walkup, and she did all of the heavy lifting. Ironically, while I was medically absolved from carrying groceries and laundry up the stairs, I was still cleared to play tennis, ski, and keep physically fit.

Stick and Stain in the Brain

The previous scientific thread left off with a description of my Procion Yellow staining of leech neurons. While I loved studying the leech, I was having mixed feelings about whether I wanted to spend my career working exclusively on a "simple" model nervous system that on closer inspection was turning out to be pretty complex!

Down the hall from the Nicholls lab, Hubel and Wiesel were immersed in their pioneering studies of visual cortex in cats and monkeys. I had first encountered their work when I read *The Machinery of the Brain* in college. At Harvard, we read many of their papers in one of the graduate reading courses. It was fascinating to read in greater depth about the functional organization of visual cortex and to discuss these issues weekly with the masters themselves. I recall musing with other students at the time as to whether Hubel and Wiesel had skimmed up most of the cream of what was to be learned about visual cortex, leaving mostly "skim milk" for the rest of us to mop up. I didn't really believe that was the case, but over time, I have converted to a complementary view in which the more we learn about any given part of the brain, the more we expose how much remains to be deciphered to achieve a truly in-depth understanding.

Aki Kaneko, a postdoc with the Hubel and Wiesel lab at that time, was making quite a splash by using Procion Yellow to elucidate structure-function relationships of bipolar cells in the goldfish retina (Kaneko, 1970). An obvious extension would be to explore structure-function comparisons in the visual cortex, especially because there was a tantalizingly appealing hypothesis to explore. One of Hubel and Wiesel's most famous hypotheses involved a "functional hierarchy," in which lateral geniculate nucleus (LGN) axons converge on cells with "simple" receptive fields, while simple cells project to (and give rise to) nearby cells having "complex" receptive fields. A natural anatomical corollary of their physiologically inspired hypothesis is that

simple cells would be concentrated in the input layer (layer 4) and should be stellate as described by classical anatomists for layer 4. Complex cells, by this hypothesis, would be pyramidal cells in superficial and deep layers.

To tackle this project, Hubel and Wiesel encouraged me to team up with Jim Kelly, who had expressed interest in the endeavor and was just finishing up his thesis research with Max Cowan at Washington University in St. Louis. Jim's solid anatomical expertise complemented my experience in neurophysiology and in working with Procion Yellow. Jim and I hit it off in our initial interactions, and we joined forces in the fall of 1971.

Hubel and Wiesel provided us with the equipment we needed, but beyond that, they had a pretty laissez-faire approach to letting new postdocs launch their projects. Neither Jim nor I previously had done any mammalian neurophysiology, but we got generous help from Jim Hudspeth and Carla Shatz in getting our rig operational and learning the ropes. Then we flew by the seat of our pants in getting intracellular recordings and dye injections under way. It was a challenge to get stable intracellular recordings from a pulsating agar-coated brain, then to characterize receptive fields as simple or complex (not as easy as David and Torsten had made it seem in their papers!), and to impale cells in a way that would inject dye into the cell without clogging on the one hand or excessive leakage on the other. Beveling the electrodes worked to keep the electrodes sharp while letting current pulses eject the electrically charged dye. If someone had suggested that within a decade patch clamping and gigohm seals would enable spectacular filling of axons as well as dendrites, I for one would have been deeply skeptical—and completely wrong.

Our dye-injection results were consistent with the original hypothesis, insofar as simple cells tended to be stellate and complex cells were predominantly pyramidal, confirming our hopes (Van Essen and Kelly, 1973; Kelly and Van Essen, 1974). Jim and I (and others) were excited by these findings, and we were invited to give seminars at various places. In general, the results were well received. When giving a talk at Caltech, I recall getting some pushback regarding our conclusion that "the majority of simple cells are stellate" just because it was a numerical majority of the cells in our relatively small sample of cells (8 out of 13). The importance of doing proper statistical analyses and being careful not to overinterpret one's experimental data belatedly began to sink in.

Neurobiology at Cold Spring Harbor

In 1971, Jim Watson, of double helix fame and then Director of Cold Spring Harbor Labs, decided to expand their famous summer courses from molecular biology and genetics into the realm of neurobiology. Watson invited Regis Kelly (at the time a senior postdoc with Zach Hall) to lead a three-week lecture course in neurobiology. Reg in turn asked Jim Hudspeth, Eric

Frank, and me to serve as teaching assistants. I jumped at the opportunity, knowing (from my earlier embryology course at Woods Hole) that summer courses of this type offer a unique learning environment. It was intellectually very stimulating to work with a great set of teaching faculty, plus "students" of all ages, including senior investigators switching fields, such as physicist George Zweig (of quark fame) and developmental biologist George Streisinger, as well as grad students and postdocs from around the world. Jim Watson's interest in the course was evidenced by his showing up for most of the lectures, sitting in the back of the room, and more often than not leafing through the *New York Times* while paying some attention to the lecture. I recall being a bit put off by this behavior, but that was before I came to appreciate that multitasking is often a reasonable compromise when dealing with the finite number of hours in a day. The next summer was a repeat performance for me, while Jim Kelly joined as one of the teaching assistants. Sharing a crowded cottage with Jim and Carolyn Kelly and their two kids during a very rainy June was part of the memorable experience. Also, this was the summer of the Senate Watergate hearings; during lunch and at breaks we were often riveted to the television outside the cafeteria, following these historic events. In future years, Cold Spring Harbor continued to expand its neuroscience portfolio, and I was fortunate to have many additional opportunities to head to Long Island for courses and scientific meetings and to serve on their neuroscience advisory board.

When You Come to a Fork in the Road, Take It

In the early 1970s, I was in no hurry to "get a job" (i.e., to take a faculty position). Instead, my aspiration was to extend my postdoctoral training beyond the two years in the Hubel–Wiesel lab. I was particularly keen to spend some time in Europe, following the example set by a number of neuroscientists, such as Mike Dennis and Dale Purves, who had worked in Europe before returning to a faculty position in the United States.

As a grad student in the Nicholls lab, I had envisioned that my long-term research would be on an invertebrate preparation—not necessarily the leech, but one that would be amenable to detailed analysis at the level of individually identifiable neurons. I initially saw the postdoctoral project on visual cortex as an opportunistic digression rather than a permanent defection from the invertebrate scene. An appealing opportunity to return to a simpler system arose when I got to know Jan Jansen, who came from Oslo, Norway, for a sabbatical in the Nicholls lab in 1969–1970. Jan and I hit it off very well at a personal as well as a scientific level. During the winter, Jan and his family introduced Isabel and me to Norwegian-style cross-country skiing in the Harvard Forest on the outskirts of Boston. The following summer (1970), Jan and family joined the entourage making the trek to the Salk Institute. Isabel and I were able to join as well. (This

involved yet another trip in someone else's Cadillac, as Isabel and I headed west in Gunther Stent's white Caddy, because he wanted it driven back to Berkeley after also having spent a sabbatical in the Nicholls lab.) Although Jan worked with Nicholls on leeches during his sabbatical year, his stated plan was to return to studies of sensory processing in the crayfish nervous system once back in Oslo. This appealed to me, and we made preliminary plans that I would spend two years in Oslo after completing my first postdoc under Hubel and Wiesel.

Once immersed in the visual cortex project, I began reconsidering my career trajectory. I became progressively more fascinated with visual cortex as a system potentially better matched to my long-term interests. Hubel and Wiesel at that time had mostly switched from the cat to studying primary visual cortex in the macaque. They identified many features in macaque V1 that were "crisper and cleaner" than in the cat, and there was also the fact that the macaque brain is evolutionarily much closer to the human brain. Sometime in 1972, Semir Zeki from University College London visited Harvard and gave a seminar on his physiological and anatomical explorations of macaque "prestriate" visual cortex. He presented anatomical evidence that area V1 was surrounded by more than just two concentrically organized areas (areas 18 and 19, or V2 and V3), and he presented preliminary neurophysiological data on functional specialization in some of these areas. I became intrigued by the prospect of diving into the relatively uncharted waters of higher visual cortex in nonhuman primates and was encouraged by Torsten and David to consider working with Zeki. I wrote to Semir to explore this possibility, and his response was enthusiastic. I then applied for and received a three-year fellowship from the Helen Hay Whitney Foundation. This was a wonderful fellowship, because it was completely flexible with regard to which labs I chose to work in during the three years of funding.

Given these developments, I became ambivalent as to whether I actually should proceed with a plan of two additional transitions in research orientation—that is, from cat visual cortex to crayfish, then from crayfish over to monkey visual cortex. Was this wise from a professional or career development perspective? Might I be shooting myself in the foot in terms of future job opportunities? I met with Torsten, and in essence asked him whether I was foolhardy, indecisive, audacious, or just plain crazy to jump back and forth from invertebrate to mammalian systems multiple times in my career. I asked accordingly whether I should revise my plan of working with Jan in Oslo for two years on invertebrates if I really planned to end up returning to the mammalian visual system. Torsten had been trained in Sweden as a psychiatrist, so he knew the real meaning of the term crazy. In his thoughtful but diffident manner, he encouraged me to stick with the game plan and pursue my postdoctoral plans with both Jansen and Zeki despite the divergent systems. It was a decision I have never regretted, as it

kept my intellectual horizons very broad, in ways that affected later parts of this story. Whether this would be good advice for someone in our current scientific climate is an interesting question. I don't have a simple answer, as scientific breadth and depth are both as important as ever. On the one hand, many experimental systems have become increasingly complex to master, and it is important not to bite off more than one can chew scientifically. On the other hand, many other neuroscientists (including esteemed contributors to this series) have been highly successful in pursuing multiple frontiers, either concurrently or in rapid succession. Moreover, there is something satisfying about stretching one's intellectual perspectives. In the end, each scientist needs to make choices that fit one's own career interests and ambitions. The imperative is to work on problems about which you are passionate and that offer opportunities to significantly advance our understanding.

Norway (1973–1975)

On a sweltering summer afternoon in 1973, Isabel and I headed to Boston's Logan Airport to begin our three-year European adventure. We almost missed our flight, because I left my sports coat containing our passports and tickets behind at a farewell party hosted by Jim Kelly, and it was a mad scramble to get back to the airport, barely in time. After a few days in London visiting Dale and Shannon Purves, we flew to Oslo. Jan Jansen met us at the airport and took us out to dinner at a mountainside restaurant overlooking Oslo. Afterward, we went for a short hike in the nearby Nordmarka forest while it was late but still bright outside, followed by a brisk swim in a cool little lake. It was a great start to two years in Norway that were in many respects idyllic at both professional and personal levels, thanks to a special confluence of circumstances.

Scientifically, my two years in Jan's lab were very productive, though we ended up working on completely different projects than the original plan (arranged back in Boston) to study crayfish neural circuitry. Our first departure from plan A was to initiate a new project on neural regeneration in the leech nervous system following peripheral nerve lesions (cuts or crushes). We found that reinnervation was strikingly specific for both sensory and motor axons, especially after a nerve crush, when the distal nerve stump was near at hand to guide returning axons. Then we decided to shift focus and study the reestablishment of neuromuscular connections in rats, in order to test whether synapses could be restored during a complete pharmacological blockade of synaptic transmission. We found that reinnervation of the rat diaphragm muscle proceeded normally even when acetylcholine receptors were completely blocked by sustained administration of alpha bungarotoxin (coupled with artificial respiration), demonstrating that synaptic transmission was not required for morphologically healthy synapses to be restored.

A third project, which turned out to be the most interesting and significant of my Oslo research, was a study of synapse elimination in newborn rat pups. In 1974, Michael Brown came to Jan's lab for a sabbatical from his faculty position at Oxford. Michael and Jan decided to follow up on some intriguing observations by Redfern (1970), suggesting that newborn rat muscles have multiple synaptic inputs instead of the strictly single synapse per muscle fiber that is a highly distinctive feature of adult skeletal muscle. They quickly confirmed Redfern's initial observations, and it became clear that there were many interesting follow-up experiments worth doing. Michael and Jan generously invited me to join the collaboration. The next few months were quite exciting, as we carried out a variety of experiments to systematically characterize the polyneuronal innervation and synapse elimination phenomena. We ruled out electrical coupling of muscle fibers and showed that motor units were many times larger (in terms of the fraction of muscle fibers innervated by individual motor axons) at birth than they were just a couple of weeks later. I found the writing of the paper on these results (Brown et al., 1976) to be the most interesting of the publications I had worked on up to that point, because of the intriguing developmental issue that arose. The reasons why muscles have this vast initial excess of synapses was (and still is) puzzling. But we were optimistic (correctly so) that this would prove to be an excellent model system for studying synaptic competition and pruning of excess synaptic inputs, as Jeff Lichtman and many others would later demonstrate.

Jan's lab was small, but his lab and the nearby scientific environment were intellectually very stimulating. Eric Frank, my graduate student colleague at Harvard, had also decided to do a postdoc with Jan, which he began in 1972, a year ahead of me. Terje Lømo (codiscoverer of long-term potentiation [LTP], when working with Tim Bliss) was also working on neuromuscular development and plasticity in the same building. Our groups interacted very closely, and Terje became a good friend. Per Andersen, a pioneer of hippocampal slice physiology, was also an excellent neuroscientist and a good colleague at the university.

Most of our Norwegian colleagues and friends spoke excellent English, but Isabel and I had started learning Norwegian while still in Boston. We continued learning and practicing our host country's language for many of our nonscientific interactions. Our life outside the lab mostly centered on outdoor activities—the Norwegian love for outdoors in all seasons was part of what had drawn us to Norway. Our apartment was on the outskirts of Oslo, right next to the Nordmarka forest that ringed the city. Eric Frank and his wife Jane lived in the apartment upstairs from us, and on weekends we often went out together, hiking in the summer/fall and cross-country skiing in the winter/spring.

Isabel became pregnant during our first year, but that didn't slow her down much from our hiking and cross-country skiing ventures. Our first

son, Scott, was born in August 1974, a day after Isabel had picked many kilos of strawberries at a nearby farm. A few days after Isabel and Scott came home from the hospital, Seymour Benzer came to Oslo to give a lecture. Jan and I had gotten to know Seymour from our summer at the Salk Institute in 1970. Seymour was a genuine food connoisseur, known for carrying a little black notebook crammed with information about restaurants and foods. Isabel and I volunteered to host a dinner party for Seymour at our apartment. (Jan at that time was living in a cottage that was too small and rustic to serve for the event.) Jan decided that the menu should highlight some fresh Norwegian crayfish, and he knew how and where to catch them. The night before the dinner party, Jan and I drove to a stream some ways out in the forest. Around midnight (once it finally got dark!), we put on rubber galoshes, waded down the middle of the stream, and used flashlights to make the crayfish "freeze" with their claws extended so as to make them easy picking. We grabbed many dozens of crayfish in a couple of hours, then headed home. The next night Isabel and I hosted the dinner party for Seymour, with strawberry shortcake accompanying the crayfish steamed with dill. I suspect the recipe made it into Seymour's notebook, and perhaps mention of our nine-day-old son as well.

Many Norwegians had a family cottage (*hytte*) up in the mountains or along the seashore, where it was traditional to spend much of their holiday time. We were extremely fortunate that many of our colleagues and friends invited us up to their family hytte to share their special Norwegian experiences. The most rustic and our favorite was Jan's hytte (Bakkevolden), which we visited several times. It was several hours northeast of Oslo and a short hike from the nearest road. There was no electricity, and water arrived only when someone lugged it up from a stream a short hike away. We had additional memorable experiences at the hyttes of Per Andersen and of several other friends we continued to visit during many return trips to Norway in subsequent years.

Our son Scott was a mellow little fellow, amiable from the outset. Two days a week, he stayed with me at the lab, staring at oscilloscopes while Isabel took a Norwegian course. Anyone walking into the lab might catch Jan and me doing an experiment at our rig, Jan with a pipe and his omnipresent dog underfoot, and me next to Scott in his pram. Isabel also learned the craft of pottery, working closely with a local Norwegian potter, Liv Keller, who has remained a close friend over the years.

London and My Start as a Cartographer

In the summer of 1975, Isabel, Scott, and I boarded a ship from Oslo to Newcastle, England. All of our belongings were crammed into our Volvo station wagon, and there was momentary angst as we watched a crane lower our car into the bowels of the ship while dangling from (what seemed to be) the most tenuous of cables.

We drove to London and settled into an apartment in Finchley Central, north of the city. Living in England was a very different experience than Norway, both scientifically and socially. We made good friends with several of the neighbors and enjoyed playing in the local tennis club, but social interactions with my academic colleagues were infrequent. Here, I focus on the scientific aspects, as this became my entrée into a career as a cortical cartographer.

In Semir's lab, the original plan was that we would study color processing in macaque area V4, following up on the findings he had presented in Boston but using a fancy new video graphics display he had just acquired. By then, he had published his earlier work and reported that all of the cells he encountered in V4 were color selective (Zeki, 1973). In the first few neurophysiology experiments in his lab, we found more of a mixture, in which many cells were color selective as expected, but many others appeared rather nonselective. However, it was unclear whether we were actually recording from area V4 as intended. This uncertainty persisted even after postmortem histological sectioning and reconstruction of electrode tracks. The heart of the problem was that the cortical convolutions were complex in the region we were exploring, as were the relationships that previously were reported between areal boundaries and the convolutions (Zeki, 1971).

After considerable discussion, I persuaded Semir to combine our neurophysiological recordings with an anatomical approach to delineating areal boundaries. Specifically, we surgically transected the corpus callosum prior to the neurophysiological recordings, then mapped the distribution of degenerating axonal terminations as a marker of the vertical midline between the left and right visual hemifields, which Zeki (1970) had previously shown to be a marker for boundaries between visuotopically organized areas.

Cortical Cartography, Part I

Around this time I became impatient and frustrated with the conventional approach of analyzing and displaying anatomical data using drawings of histological section contours taken at irregular intervals through the brain (typically accompanied by side-view sketches of the brain with lines showing the level at which sections were taken). This approach forced readers to conjure up a three-dimensional (3D) mental image of what the topology and spatial relationships were. I found it very difficult to evaluate data spread across multiple sections within a single hemisphere or to compare results across different brains.

In mulling over the problem, I harkened back to an important paper I had learned about from David Hubel several years earlier, during an informal discussion at one of the afternoon tea breaks Hubel and Wiesel routinely held in the common room next to their lab. In the context of discussing their own ongoing work on macaque area V1, Hubel mentioned a beautiful study published a decade earlier by Daniel and Whitteridge (1961), who dealt

with the convoluted configuration of the macaque primary visual cortex (V1) by proposing a mathematical transformation of V1 and its visuotopic organization using a quasi-ellipsoidal flatmap representation. Daniel and Whitteridge also generated a physical "inverse transformation" in which they took a smooth sheet of plasticene (clay) as a model and folded it into the approximate shape of a real calcarine sulcus; then they physically sliced the convoluted model and thereby replicated the appearance of the calcarine sulcus in histological sections. I recall Hubel concluding that area V1 is (sort of) like a football that has been split in half (a half-football for each hemisphere), then deflated by crumpling to fit inside the skull. I was intrigued, but had no glimmer at the time how important this conversation would become as a personal and practical introduction to cortical cartography.

Recalling Hubel's comments from the Harvard days, it struck me that a solution to our conundrum in London would be to make a map that would flatten out the convoluted monkey prestriate cortex, analogous to what Daniel and Whitteridge had done for area V1. Indeed, Hubel and Wiesel (1972) had already started down that path by generating straight-line contour maps in order to flatten out small portions of primary visual cortex from their histological data. I started down the same road, using pencil and tracing paper to straighten out the contours of histological sections through monkey prestriate cortex in the region Zeki and I were mapping. However, it soon became apparent that the straight-line approach was fundamentally inadequate, given the complex folding in the region we were studying, where the lunate sulcus and the inferior occipital sulcus run close to one another. Moreover, for a short while, it appeared that this mapping effort might be further confounded by virtue of an observation suggesting that there is a physical "tunnel" between two neighboring sulci (the lunate and inferior occipital sulci; Zeki, 1971, Fig. 8). If correct, it would imply that the macaque cortex is topologically equivalent to a donut! Zeki and I reexamined the histological sections in question and determined that there was actually no "intersulcal tunneling" after all. Reassured that all was well topology-wise, I returned to my efforts to manually flatten the cortex.

Toiling away in my windowless office at University College London, I struggled for weeks using pencil and tracing paper to manipulate the shapes of magnified section contour drawings. Extensive trial-and-error efforts grudgingly yielded primitive flatmaps that spanned limited regions of convoluted cortex and met two key criteria: (a) preservation of topological relationships (no crossing over of contours) and (b) avoiding severe areal distortion (i.e., excessive scrunching or stretching between contour lines). During this period, Semir and I often went to lunch together, and I would update him on the progress of this effort. I think it is fair to say that he was tolerant but less than fully on board with the need for this effort. In the end, we published one major paper from the combined neurophysiology, neuroanatomy, and flat-mapping efforts (Van Essen and Zeki, 1978). The paper

introduced area V3A, the first of many visual areas that I had a role in identifying. The cartography story picked up again at Caltech, but first there are other topics to consider, including how I ended up on the Caltech faculty.

Landing Back at Caltech

Some of the events that eventually brought me back to my undergraduate alma mater occurred in the spring of 1973, before I headed off to Europe. Jim Kelly and I went on a joint road tour, giving talks at several institutions, including Wash U, Caltech, and UCSF, which had expressed interest in our research. It was a bit awkward, because Jim and I had worked closely together and wanted each to share equal credit for our joint effort, but our hosts didn't want a tag-team seminar. We worked it out by alternating, with one of us giving a seminar on our common postdoctoral work and the other giving a talk on his thesis research. By the time I headed to Norway, there were no firm offers, but some informal good "vibes" made it seem that job prospects were encouraging.

Isabel, Scott, and I returned to the United States for several weeks in the summer of 1975, including a memorable Cold Spring Harbor symposium on the brain, followed by visits to the three institutions where job offers had emerged: Harvard, Stanford, and Caltech. The lure of Harvard was great, where I had spent six wonderful years and had the opportunity to interact closely with Hubel and Wiesel and other esteemed colleagues. Stanford was highly attractive, in part because of the Bay Area milieu, but also because John Nicholls had moved there and Max Cowan was about to become chair of the department. Caltech was attractive as well, even though I had never felt a specific hankering to return to my alma mater. What appealed to me most about Caltech was a new building devoted to neuroscience (Beckman Behavioral Biology Labs, made possible by a generous Caltech benefactor, Arnold Beckman), with great colleagues, such as Mark Konishi, Jack Pettigrew, and John Allman, plus Jim Hudspeth and Jim Kelly who were about to accept offers for faculty positions. In addition, when I expressed an interest in being able to set up a lab that would enable continuation of my split focus (primate visual cortex and neuromuscular development), Bob Sinsheimer, the Biology Division chair, didn't hesitate to make a commitment to enable that opportunity. Finally, much as I respected my former mentors, my instincts told me that I might be better off to set off on my own path. In the fall of 1975, I agreed to return to my old stomping grounds at Caltech the following summer.

Caltech (1976–1992)

In the summer of 1976, my family (including baby Scott and pregnant Isabel) headed west to southern California, and I joined the Caltech faculty.

On the home front, we soon found a house in Pasadena that would remain our abode for the next 16 years. In December 1976, Isabel delivered Brian, our second son. (Once again, childbirth was linked to a lab-related event, as we had hosted postseminar dessert for Darwin Berg the evening before Isabel went into labor.) Brian was as colicky as Scott was mellow. Their personalities remained very different, but they grew up as close friends and have become outstanding adults and parents.

Before delving into my research program at Caltech, it's worth commenting on the neuroscience community in those early days. The Caltech neuroscience faculty continued to grow in the late 1970s and early 1980s with the recruitment of Jeremy Brockes, Mary Kennedy, Paul Patterson, David Anderson, and later many others. Weekly NeuroLunch and monthly NeuroDinner events helped build a strong sense of community. I especially enjoyed the local environment on the third floor, with close interactions of my lab with students and postdocs in the Konishi and Hudspeth labs. Unfortunately, things did not work out well for Jim Kelly (a complex and sad story). After he moved on, Howard Berg joined the faculty, and for a while, my lab was sandwiched between biophysicists doing pioneering work on hair cells (Hudspeth) and bacterial motors (Berg). On the teaching front, Jim Hudspeth and I began many years of teaching the introductory neurobiology course (Biology 150). It was the successor to the course that had inspired me when taught by Felix Strumwasser, Antonie Van Harreveld, and Cornelius Wiersma back in 1966. Our "Bi 150" course proved to be popular, and it was particularly enjoyable because we had bright and intellectually curious students, plus great graduate student teaching assistants year after year. Coming up with thought-provoking, out-of-the-box homework and exam questions was challenging but especially enjoyable. I also led a graduate reading course in developmental neurobiology, which helped broaden my developmental perspective in ways that in due course impacted my own research.

On the research front, my lab at Caltech launched into our two-pronged effort to concurrently study macaque visual cortex and mammalian neuromuscular development. The next four sections focus on themes related to visual cortex: neurophysiology, anatomy and connectivity, cortical cartography, and neural computation. Our efforts on neuromuscular synapse elimination and development are covered later, in conjunction with developmentally oriented research I continued at Wash U.

I was very fortunate to recruit two talented Caltech graduate students early on. John Maunsell worked on the anatomy and physiology of visual cortex. John Bixby did his thesis work on neuromuscular development but also made important contributions to our early studies of visual cortex. (I muffed an initial chance to recruit Bill Newsome as well, but later he joined the lab as a postdoc after doing his thesis with John Allman.) We set up a neurophysiology rig for acute monkey recordings, initially not much

fancier than what Hubel and Wiesel or Zeki had in their labs. In an initial study, we used these conventional approaches to examine the "motion selective" area in the superior temporal sulcus (STS), which Zeki had originally described but not named (Zeki, 1974). In a review for *Annual Review of Neuroscience* (Van Essen, 1979), I had proposed that this be called area MT (the middle temporal area) in the macaque because of its likely homology (i.e., common evolutionary origin) with area MT that John Allman (my colleague downstairs) and Jon Kaas had reported in the owl monkey a few years earlier (Allman and Kaas, 1971). This proposal didn't sit well with Zeki, who published a paper asserting (based on thin evidence, I felt) that a homology of this area in owl monkey and macaque was most unlikely, instead intimating that the macaque area should instead be called V5 (Zeki, 1980). The evidence in favor of a homology was further buttressed by a subsequent anatomical and physiological study with Maunsell and Bixby (Van Essen et al., 1981), in which we reported important similarities in myeloarchitecture and topographic organization for MT in the two species. To this day, the most intensively studied macaque extrastriate area is variously known as MT, V5, or the hybrid term "MT/V5," depending largely on which camp and continent one is affiliated with!

My postdoctoral training in visual neurophysiology had emphasized qualitative rather than quantitative approaches to analyzing and reporting receptive field properties. This bias was most colorfully articulated by David Hubel, who famously declared that "if you need to do statistics on your data to know whether the results are significant, then the results are probably not very interesting." However, my perspective changed once at Caltech. I became convinced that visual cortex was far too complex to be adequately understood by mainly subjective and qualitative assessments. While I felt strongly that the time was ripe to shift to quantitative computerized experiments, I personally had only limited experience with computers and programming. Fortunately, Jim Hudspeth and I teamed up and convinced our chairman, Bob Sinsheimer, to buy us a computer that we shared between our (adjoining) labs for many years. Once our shiny new PDP-11/34 arrived, it was necessary to code everything from scratch, but fortunately John Maunsell proved to be extremely facile in programming the requisite software for neurophysiology data acquisition and analysis.

We also needed customized hardware for generating visual stimuli that could be systematically varied in size, orientation, speed, direction, color, and disparity. We enlisted the efforts of a superb Caltech engineer, Herb Adams, who was amazingly gifted at designing and building customized equipment for highly specialized purposes, based on verbal instructions and no need for detailed blueprints. Herb had previously done wonders for Mark Konishi and Jack Pettigrew in building customized hardware for visual and auditory experiments in their labs. The auditory spatial localization device

for the Konishi lab was respectfully known as "Herb's Hoop." The system he built for my lab didn't get a name, but it did include a 1,200-watt projector (cooled by a large fan) to let enough light through our narrow-band color interference filters. Electronic control devices linking the optical projector to our computer were made by Mike Walsh, another excellent engineer. This system served the lab well for a decade, until we transitioned to video graphics displays for stimulus generation.

Duly armed with our computer-controlled visual stimulation system, John Maunsell carried out the first quantitative studies of receptive field properties in macaque MT. He confirmed the high incidence of direction selectivity and quantified the tuning for speed and binocular disparity in this area. This was a major part of his thesis, but it was only half the story, as there is an anatomical part to follow.

Several talented postdocs joined the lab in the early days, including Ted DeYoe, Bill Newsome, Andreas Burkhalter, and Dan Felleman. Most of the ongoing projects used anatomical and physiological methods in combination to characterize the location, functional properties, and connectivity of several areas, including V2, V3, VP, V4, and MT. Together with the two Johns (Maunsell and Bixby), we made complementary advances on several broad fronts that warrant further consideration: cartography (flatmaps), hierarchies, and processing streams.

Cortical Cartography, Part II: From Pencil and Tracing Paper to the Birth of Computerized Cartography

Cerebral cortex is a thin sheet of gray matter that is convoluted to varying degrees in different species. Convolutions allow a large surface area to be crammed into a compact cranial vault, much as one crumples a sheet of paper to fit it into a small box. The developmental question of how the cortex "gets its folds" comes later in this story. In this section, the focus is on the methodological advances needed to represent the cortical sheet, initially by purely manual methods, but eventually succumbing to computerized methods of reconstruction, inflation, and flattening.

Soon after arriving at Caltech I wrote a grant proposal emphasizing our plans to capitalize on the pencil-and-tracing-paper cortical flat-mapping method I had developed in London. I proposed it as a workhorse method for analyzing and displaying anatomical connectivity data as well as physiological recording sites in various extrastriate visual areas of the macaque. After submitting essentially the same grant concurrently to NIH and NSF (as was allowed in those days), feedback came first from NSF in the form of seven written reviews plus a summary statement. In general, the reviews were very positive, but the majority had one common criticism. Simply put, most reviewers strongly disliked my new flatmap approach; the critiques can be paraphrased as, "the flat maps the PI proposes to use for displaying his

results are incomprehensible and detract from an otherwise fine proposal." Had I followed the majority opinion, I would early on have abandoned the flat-mapping approach altogether. On the other hand, National Eye Institute (NEI) enthusiastically funded my grant, and many other colleagues were supportive of our mapping approach.

An important milestone was reached when we extended the original method to generate flatmaps of the entire cerebral hemisphere (Van Essen and Maunsell, 1980). A small cottage industry sprung up in the lab, reflecting the time-consuming demands of processing data from every monkey experiment in which recording sites and/or tracer injections were carried out (usually it was both). We systematized the process for localizing recording sites and the distribution of retrograde and anterograde tracers by viewing histological sections under the microscope and manually plotting the data onto photographic enlargements of each section. A large draftsman's table served as the focal point for generating pencil-and-tracing-paper flatmaps from photographic enlargements of histological sections, and then transferring anatomical data from photographs onto the flatmaps with submillimeter accuracy. Over time, shelves in the lab became crowded with primary data (slide boxes), binders containing the enlarged photos, and sliding drawer cabinets filled with many large flatmaps in various stages of preparation.

We used these flatmaps not only to study extrastriate cortex, but also for analyses of area V1, including its topographic organization (Van Essen et al., 1984) and the complete pattern of ocular dominance stripes (LeVay et al., 1985). We even slipped transiently into the netherworld of the LGN to map the retinotopy of all its layers (Connolly and Van Essen, 1984).

Even though there was growing acceptance of cortical flatmaps as a method for analysis and visualization, our methodology was slow to catch on in other neurophysiology and neuroanatomy labs. The main problem was that flatmaps were laborious to generate and required expertise that was not easy to obtain without hands-on training. Gattass and Gross (1981) developed an alternate method using physical unfurling of 3D wireframe models, but this wasn't particularly easier or more accurate. The Ungerleider and Desimone lab ended up using both of these methods (Ungerleider and Desimone, 1986a, 1986b).

It was crystal clear that the entire cortical reconstruction and analysis process was a job that needed to be handed over to computers. My initial encounter with this notion had come in the early 1970s, in a story that once again involves David Hubel. Not long after he had waxed eloquent in the Harvard common room about the clay model of primary visual cortex made by Daniel and Whitteridge, Hubel expressed an interest in using computers to generate 3D reconstructions of area V1 in the convoluted calcarine sulcus that he and Torsten were studying in the macaque. Since they hadn't yet gotten a computer in their own lab, Hubel decided

to spend several weeks working on the problem using a "high-power" computer Sydney Brenner made available in Cambridge, England. Soon after his return, I recall Hubel grumbling about how it was a much harder problem than he had envisioned. This turned out to be an understatement, to put it mildly! But my exposure to his experience had planted a seed, and I was keen to begin moving forward on this once I set up my lab at Caltech.

Obviously, the computers needed proper instructions (algorithms and code) in order to get the job done. This was far easier said than done, but little did I realize that it would take nearly two decades for such a seemingly simple concept to become a practical reality. The first part of the puzzle was to reconstruct a 3D model of the cortex based on information contained in a set of two-dimensional (2D) images obtained from histological slices. My first stab at the problem was in the late 1970s, when I teamed up with Gilbert McCann's group at Caltech to reconstruct a chunk of macaque occipital cortex (see Van Essen, 2012, Fig. 1). However, surface generation and visualization were painfully slow, even though we were using state-of-the-art surface rendering software and the latest hardware (McCann's PDP-10 computer). A decade later, my lab acquired a state-of-the-art Silicon Graphics Inc. (SGI) computer that had much better surface rendering capabilities (to the tune of $80,000, a whopping price at the time!). With considerable effort, my student George Carman and our programmer Dave Bilitch implemented a first-generation surface reconstruction program (called "anatomy"). The second part of the puzzle was to generate a flatmap of the cortex, given the information contained in a 3D model. Hence, in parallel, George tackled the cortical flattening problem. He implemented an algorithm based on simulated annealing that could indeed flatten area V1, but it was painfully slow and didn't scale well with larger cortical expanses such as an entire hemisphere. We learned to appreciate the serious computational challenges of generating accurate surface reconstructions and flatmaps (Carman, 1990; Carman et al., 1995). Around the same time frame, other groups implemented alternative approaches to the cortical flattening problem (Schwartz et al., 1989; Wolfson and Schwartz, 1989; Dale and Sereno, 1993). This marked the beginning of a new era for the field, but my part in this story takes place mostly at Wash U and is covered later.

Hierarchies and Processing Streams

The story now reverts to the early 1980s. John Maunsell's thesis research on physiologically characterizing MT receptive field properties was complemented by an analysis of cortico-cortical connectivity after injection of retrograde and anterograde tracers into MT. John's results provided evidence for several newly identified visual areas as well as many previously unreported anatomical pathways. As he was trying to wrap this up and write his thesis,

I recall challenging him to go beyond simply cataloging these new areas and pathways, but instead to strive for a broader synthesis. One Saturday morning I came into the lab, and John excitedly (especially for him!) asked me to come to his office. The night before, he had sketched out on his office chalkboard a schema for what turned out to be the first anatomically principled visual cortical hierarchy. He built upon observations by Rockland and Pandya (1979), that feedforward and feedback pathways have distinct laminar patterns of connectivity. Applying these pairwise relationships to known connectivity of MT and other areas resulted in an orderly hierarchy, based on 13 areas and six hierarchical levels, inferred from 36 pathways incorporated into this initial version.

At that time, many neuroscientists equated the notion of a neurobiological "hierarchy" with the unidirectional "serial hierarchy" proposed by Hubel and Wiesel for physiological cell types, in which (as described already) LGN axons made synapses onto cortical simple cells, which in turn converged onto complex cells, which in turn converged onto hypercomplex cells (Hubel and Wiesel, 1962, 1965). We decided to use the same term, but to generalize its usage to reflect an appropriately broader definition of a hierarchy as a system in which each component (cortical area) has a well-defined position (higher, lower, or equal) relative to the others. Our proposed anatomically based hierarchy embraced several key features, including (a) feedback as well as feedforward pathways, (b) multiple areas at a given hierarchical level, and (c) pathways that traverse more than one hierarchical level (Maunsell and Van Essen, 1983; Van Essen and Maunsell, 1983). In the meantime, some local pundits (notably including Bill Newsome) speculated that MT actually stood for Maunsell's thesis.

John's initial hierarchical scheme underwent substantial evolution and expansion over the subsequent decade. One important set of developments centered on the discovery of anatomically and functionally distinct modules within early visual areas (V1 and V2) and the hypothesis of parallel processing streams that a number of labs were exploring around that time. Livingstone and Hubel (1984) reported that V1 included an array of "blobs" having low orientation selectivity and high color selectivity (and somehow overlooked in earlier studies of orientation columns); these were surrounded by "interblobs" that were high in orientation selectivity and low in color selectivity. These modules in V1 showed specific patterns of connectivity with a coarser tripartite pattern of "stripes" in V2 (Livingstone and Hubel, 1984). Ted DeYoe and I used dual tracer injections, one into V4 and another into MT, to demonstrate that the V2 stripes are distinct from one another in their connectivity with areas V4 and MT and in their physiological characteristics (DeYoe and Van Essen, 1985); similar results were reported by Shipp and Zeki (1985). We later provided evidence for modularity at higher levels, within V4 and adjoining inferotemporal cortex (DeYoe et al., 1994).

These and other studies around that time linked the cortical processing streams to specialized subcortical channels, particularly the parvocellular (P), magnocellular (M), and koniocellular (K) cells in the retina and LGN. A seductive hypothesis (the one-stream, one-function point of view) was popularized, in which each processing stream was distinct from the others both functionally and anatomically, and was highly specialized for processing motion, form, and color respectively (Livingstone and Hubel, 1984; Shipp and Zeki, 1985). There was indeed experimental support for this hypothesis, especially if one looked at the data selectively. However, my lab emphasized from early on that cross-talk between processing streams also occurs and is fundamental to a deeper understanding of visual processing (Van Essen and Maunsell, 1983). We promoted an alternative perspective of "concurrent processing streams" (DeYoe and Van Essen, 1988) that gradually emerged as we incorporated a computational and psychophysically motivated perspective into our efforts, as discussed in the next section.

We continued to push forward on the cortical hierarchy front. I extended the analysis of visual cortex parcellation and connectivity in a chapter on visual cortex, part of a book series on Cerebral Cortex edited by Alan Peters and Ted Jones (Van Essen, 1985). The visual cortical hierarchy in that version had grown to 17 areas linked by 92 pathways. In 1990, I was invited to write a review on visual cortical organization for the journal *Visual Neuroscience*. I asked Dan Felleman to work with me on further updating the Maunsell and Van Essen (1983) and Van Essen (1985) versions of the hierarchy, given the many studies on cortical connectivity that had since been published. Plowing through the relevant literature turned out to be an arduous effort in which Dan and I each spent hundreds of hours in the library (what a quaint thought, nowadays!) and in our offices, trying to make sense of complex and often ambiguous figures or statements in hundreds of papers. As we began writing the review, we generated a revised visual hierarchy and parcellation that included 305 pathways among 32 areas that are largely visual in function. We also extended the parcellation to the entire cerebral cortex and the analysis to include a hierarchical scheme for somatosensory and motor cortex as well. It thus became clear that this was a story about cerebral cortex in general and not just visual cortex on its own. We ended up submitting our manuscript to the newly launched journal *Cerebral Cortex* (after apologizing to the *Visual Neuroscience* editor for jumping ship). It became not only the inaugural article of the new journal but also my most widely cited publication by far (more than 5,000 citations to date). The "Felleman and Van Essen" flatmap is imprinted on a T-shirt and was the centerpiece of a large 50th-birthday cake made by Isabel. The iconic subway-chart hierarchy is imprinted on a unique tie given to me by Erin Reid, which I wear on special occasions!

In subsequent years, I was occasionally asked whether I was planning to update the cortical hierarchy to incorporate another round of

recently reported cortico-cortical pathways identified in the literature. My response was that I flat-out refused to consider an update to the monkey connectivity analysis by the same approach of poring over the literature to extract qualitative assessments of connection strength and areal boundaries. Instead, I was keen to shift our efforts in a direction that would enable more quantitative and precise assessments of the complexities of cortical circuitry. Key methodological advances that were needed included (a) automated surface reconstruction and flattening, (b) quantification of connection strengths to supplant the qualitative assessments or impressions from images, (c) improved intersubject registration, and (d) more accurate cortical parcellations. Over the next two decades, my lab would contribute to progress on each of these fronts, but it has been a long and unexpectedly challenging endeavor. It has also been highly rewarding, especially toward the end of the chapter. But next we switch back to neurophysiological themes, with a strong dose of computational and psychophysical perspectives included.

A Computational Perspective—Beyond Bars and Edges

The Hubel–Wiesel school of cortical function in which I was trained had promulgated the use of bars and edges as core visual stimuli used for visual neurophysiology. These had proven spectacularly successful for probing V1 and other early areas, and we got a lot of mileage exploiting them for many years and many studies of extrastriate visual areas in my lab. However, they were obviously inadequate for probing more complex aspects of form processing. Alternative types of visual stimuli were available in the early 1980s, but each had its limitations. One came from the spatio-temporal school, which used gratings of variable spatial and temporal frequency to characterize cells in ways that complemented what one could learn using bars and edges. While I had come to appreciate the strengths of the spatio-temporal frequency approach (overcoming a bias against it inherited from my mentors), conventional sinusoidal gratings lacked the flexibility to probe more complex spatial shapes. A third approach promulgated by Charlie Gross, Keiji Tanaka, and others was to use a potpourri of complex and sometimes ethologically relevant stimuli such as faces, squares, circles, and bottlebrushes. While these yielded intriguing observations, they weren't appealing as a way for my lab to go forward, given that the stimuli and stimulus spaces were difficult to parameterize and explore systematically.

Over the two decades between the mid-1980s and the mid-2000s, many talented students and postdocs in my lab studied a diverse set of neurophysiological topics relating to visual form, motion, depth, color, and attentional processing. This section includes a historical background on how we came to explore these topics, and it aims to put them in a broader computationally and psychophysically oriented perspective. Many of the projects discussed

here were done partly or entirely after our move to Wash U; thematic continuity has trumped a parsing into geographically chunked segments.

My association with computational and psychophysical approaches to vision has a number of diverse roots. Two of them involve long-term collaborations with senior investigators, Bela Julesz and Charlie Anderson (the latter story comes a bit later). These collaborations were supported by a grant I was fortunate to receive from the Office of Naval Research (ONR), which was very important in letting our research program branch out from the ongoing neuroanatomical and neurophysiological efforts supported by the NEI. Other influential factors included my extended participation in the southern California Helmholtz Club and in Caltech's interdisciplinary Computation and Neural Systems (CNS) graduate program.

Bela Julesz (now deceased) was a psychophysicist whose home base was at Bell Labs in New Jersey. Our interactions started when he came to Caltech in the early 1980s as a Fairchild Distinguished Scholar to give a series of lectures on stereoscopic depth perception (he pioneered the use of random-dot stereograms) and on texture vision. Using visual stimuli that included large arrays of oriented texture elements, Bela had formulated a "texton theory," hypothesizing that these texture elements represented fundamental elements of visual perception. I was not enamored of the texton theory, but Bela's psychophysical observations were intriguing, and they provided a valuable entrée into more complex categories of stimuli for neurophysiological experiments. We struck up a collaboration to link psychophysics with the neurophysiology of texture processing. Starting in the mid-1980s, Bela came to Caltech annually for several months during the winter to teach and do research. Bela was a complex character, fond of telling jokes in his heavy Hungarian accent. He qualified as a "high-maintenance" collaborator insofar as his large ego needed regular stroking, but our collaboration thrived for the remainder of my time at Caltech. Bela and I jointly mentored a number of postdocs (Dov Sagi and others) who carried out psychophysical studies at Caltech. On the neurophysiological front, we began several psychophysically inspired projects, including examination of neural responses to texture contrast in area V1 (Knierim and Van Essen, 1992) and to moving texture patterns in area MT (Olavarria et al., 1992). These efforts were also important from a methodological perspective. It brought us into the realm of using computer-generated visual displays—thanks to a lot of effort from Ted DeYoe and our programmer, Dave Bilitch.

Jim Knierim's project represented our first foray into alert macaque recordings, which would later become the dominant component of our neurophysiology research. It took a lot for Jim to learn the ropes, as there wasn't a nearby lab doing alert macaque recordings. In retrospect, it might have been helpful if I had taken a sabbatical to learn more of the ins and outs in a lab that routinely did alert monkey training and neurophysiology. But I have always had many scientific and administrative balls in the air

on the home institutional front and have never arranged for even a brief sabbatical—to Isabel's disappointment, as I am occasionally reminded.

Another influential development was a decade-long participation in the Helmholtz Club, a gathering of vision neuroscientists in Southern California, held monthly for an afternoon and evening at UC Irvine, near the group's geographic center. The Helmholtz Club was organized by Francis Crick and several others in 1982, a few years after Crick had come to the Salk Institute and turned his attention to neuroscience. One of Crick's lasting contributions to neuroscience was to catalyze wide-ranging, intense discussions that brought together investigators with diverse neurobiological, psychophysical, and computational perspectives, as epitomized by the Helmholtz Club (see Aicardi, 2014, for an informative history).

On the Caltech computational front, an important early seed involved the recruitment of John Hopfield, a theoretical physicist from Princeton whose interests had turned to neuroscience. Murph Goldberger, the president of Caltech, had come from Princeton and felt that it would be a great idea to recruit Hopfield to Caltech. The biology faculty were initially lukewarm about having a theoretical neuroscientist in their midst, so it ended up that Hopfield was recruited to the Chemistry Division. Not long after his arrival in 1980, Hopfield and I met for an exploratory conversation in hopes we could find common intellectual ground for a more sustained dialogue. However, we didn't speak a common language and couldn't find much traction initially. This "impedance mismatch" would change markedly over the next several years. For starters, reading David Marr's book, *Vision* (Marr, 1982) had a major impact on my thinking. In broad strokes, Marr articulated the importance of jointly considering three key aspects of vision: what are the computational tasks that need to be solved, the algorithms needed to accomplish the tasks, and the neural "hardware" that implements the algorithms? He also emphasized the highly inferential nature of vision as a process for generating percepts of a rich 3D world from a pair of 2D images. I considered Marr's book very insightful, but it wasn't immediately clear how we should adapt my lab's experimental approaches to incorporate a more computational perspective.

Ted DeYoe and I had many discussions in which we strove to incorporate Marr's conceptual framework with our perspective on the neuroanatomy and neurophysiology of cortical modules and processing streams. These discussions evolved into an article on "concurrent processing streams," which we wrote for *Trends in Neurosciences* (DeYoe and Van Essen, 1988) and which occupies a special niche when I reflect on my various reviews and perspective articles. Ted and I argued that the relationship between low-level sensory cues and the higher-level attributes inferred by perceptual processes can be subdivided into a set of "Marr-style" computational strategies, such as structure from motion, shape from shading, and various other tasks. These strategies are presumably represented algorithmically

by neural subsystems within an overall hierarchy that benefits from cross-talk and interactions among the anatomically identified processing streams. This didn't by any means resolve the key questions, but I found it an appealing way to begin getting a better handle on observed anatomical and neurophysiological complexities.

In 1984, Caltech recruited Jim Bower to the neuroscience faculty as an experimental neuroscientist working on olfactory cortex. I got to know Jim extremely well, starting from early on because Isabel and I hosted his family (with two young kids) at our house for a couple of weeks once they arrived in Pasadena and were looking for housing. Also, Jim set up his lab right next to mine, in the space vacated when Jim Hudspeth moved to UC San Francisco. Jim (Bower) and I shared a growing interest in neural computation and had frequent conversations on that front.

Around that time, John Hopfield teamed up with Carver Mead (an engineer and pioneer in VLSI computer chips and "neuromorphic computation") to teach a course on the Physics of Computation at Caltech. This morphed into a year-long triplet of courses when Richard Feynman joined the chorus the following year. The ensuing buzz around campus about the promise of interdisciplinary approaches to studying the brain motivated the Caltech administration in 1986 to endorse the creation of the Computation and Neural Systems (CNS) graduate option (training program; see https://en.wikipedia.org/wiki/Computation_and_Neural_Systems). This included the recruitment of Christof Koch, a talented postdoc of Tomaso Poggio at MIT. In an amusing déjà vu of Jim Bower's arrival, Christof and his family (again with two young kids) also stayed with Isabel and me when they arrived in Pasadena and were looking for housing.

John Hopfield served as leader of the new CNS program, and I took on the role of option representative, which included administrative responsibilities in overseeing the graduate program. Christof and Jim were energetic, irrepressible, and charismatic characters, distinct from one another. Together they became a dynamic duo who helped energize and make the CNS program really take off in terms of recruiting talented graduate students keen to work at the interface of computation and neuroscience.

In 1988, Christof and Jim organized a computational neuroscience course at Woods Hole (which is still going strong after 28 years, with fresh leaders every five years!). I enjoyed giving lectures in this course for the first couple of years. It was another great opportunity to bring my family to the east coast (where we had friends and relatives), live in a cottage near the beach, and be immersed in an intensive summer course experience (oh, yes, and to thrive on the famous peppermint ice cream at a little shop called Jimmy's!).

Back on the Caltech front and a few years earlier, I struck up a collaboration with Charlie Anderson, a physicist and engineer from RCA Labs, near Princeton. It started in 1984, when Charlie did a sabbatical in John

Hopfield's lab. Charlie had been working on machine vision using insights gained from human psychophysics. He and his RCA colleagues had implemented sophisticated image-processing algorithms to efficiently extract useful information from natural visual scenes. Charlie stopped by my office one day to introduce himself and to ask if we could talk about vision. We struck up a conversation that turned into a collaboration extending over more than two decades. It turned out we had a natural complementarity, insofar as Charlie's expertise in physics and engineering and interest in neuroscience meshed with my expertise in the latter and interest in the former. There was still a communications barrier, especially initially. Charlie thinks deeply at a high level of abstraction; one of his favorite aphorisms extends the vintage "a picture is worth a thousand words" to "an equation is worth a thousand pictures!" My forte is in the neurobiological nuts and bolts, and though I love and respect equations as well as words, I am more comfortable with the latter. At a personal level, we found it amusing to realize that Charlie had gotten his BS from Caltech and his PhD from Harvard both exactly 10 years before me. A strong friendship also grew, not only between Charlie and me but also between our spouses, Pat and Isabel.

From the outset, Charlie was a strong proponent of the view that the nervous system as a whole is extremely well engineered. This can be appreciated most readily in peripheral sensory structures (e.g., eyes and ears) where detection (sensitivity) and discrimination approach what the laws of physics will allow. Inside the skull, Charlie argued that the brain is not just a "bag of tricks" as advocated by some (Ramachandran, 1985). Instead, it must use very sophisticated information processing strategies that reflect evolutionarily driven good engineering, even though the underlying computational principles are more challenging to decipher. These ideas resonated with me, and over the years, we found common intellectual ground in talking about the engineering as well as the neurobiology of the visual system at many levels, from the retina, through V1, and to higher-level visual processing.

One of Charlie's provocative early ideas was based on the notion that dynamic routing of information, regulated by specialized control circuitry, must be fundamental to the workings of the brain, including the visual system. He proposed a novel computational construct, which he called "shifter circuits," that he initially proposed could mediate the phenomenon of directed visual attention. These ideas initially struck me as somewhat implausible in terms of how they might be wired in real neural circuits. But the more we discussed this, the more I was persuaded that there must be something to it. The feedforward anatomical connectivity of visual cortex, with its progressive convergence at successive hierarchical levels, simply can't explain many of the profoundly dynamic aspects of visual perception.

Once Charlie returned to RCA labs in Princeton after his sabbatical year, we continued our collaboration long distance, and I stayed with

Charlie and Pat a couple of times while I was on the east coast. We published our first paper together in *Proceedings of the National Academy of Sciences* (PNAS; Anderson and Van Essen, 1987) proposing three distinct ways in which shifter circuits might operate at different levels to (a) stabilize depth perception despite empirical evidence of inherent "instabilities" in alignment of the two eyes, (b) compensate for motion blur (why do we have sharp percepts of moving objects despite spatio-temporal blurring as they streak across the retina?), and (c) mediate directed visual attention (how do we focus our visual attention on a tiny fraction of the information contained in visual images, while adjusting the location and spatial scale at which attention is directed from moment to moment?).

In 1987, Charlie and Pat moved to Pasadena, so that Charlie could work primarily at the Jet Propulsion Lab (implementing a multiresolution imaging system for the Mars Rover) but also have a part-time faculty appointment at Caltech to continue our collaboration once again at close range. Many of our early perspectives were summarized in a book chapter (Van Essen and Anderson, 1990) that provides a more in-depth analysis of several fundamental aspects of visual system organization, function, and dynamics, from retinal representations through higher visual processing. Bruno Olshausen joined the lab as a CNS grad student jointly mentored by Charlie and me. Bruno expanded on Charlie's computational model of shifter circuits for visual attention (Olshausen et al., 1993, 1995). We also proposed useful ballpark estimates relating to key information bottlenecks in the visual system (Van Essen et al., 1991; see also Anderson et al., 2005): (a) at the front end, the optic nerve conveys only about 2% of the spatial information available in retinal images; and (b) at high levels, directed visual attention at any one moment accesses much less than 1% of the information transmitted via the optic nerves—it effectively "sees" a $\sim 30 \times 30$ array of "sampling elements" that shift dynamically in location and spatial scale.

Ed Connor joined the lab in 1989 as a postdoc (starting at Caltech, then moving to Wash U) to carry out neurophysiological tests of the shifter circuit hypothesis. Ed demonstrated dramatic attentional effects in V4, much larger than typical attentional modulatory effects reported before or since (Connor et al., 1997). This is important in view of the numbers just cited regarding the narrowness of the "attentional bottleneck." The effects Ed reported supported the shifter circuit model in broad strokes, though there were complexities that weren't easy to reconcile with a simple version of the model. Chris Eliasmith's group has recently extended Bruno's shifter circuit attentional model with a more neurobiologically plausible spiking neuron model (Bobier et al., 2014) that includes population coding and the neural engineering framework discussed later (Eliasmith and Anderson, 2003). However, much of the "attention" of the visual attention field has mainly "shifted" in other directions relating more to phenomena such as temporal synchrony and interactions across frequency bands (e.g., Baldauf

and Desimone, 2014; Landau et al., 2015). These are important phenomena, but the jury is still out regarding which approach will provide deeper explanatory power for directed visual attention.

In 1990, I was invited to talk at a Cold Spring Harbor Symposium on the brain. As it happened, my talk was scheduled for the late evening, at the end of an exhilarating but exhausting day of excellent presentations. I was trepidatious about giving the talk, as I feared that my words might be drowned by loud snoring from a very sleepy audience—especially because I had crafted a jam-packed overview, filled with lots of facts as well as perspectives. But the feedback I received was very positive, and I was pleased that an editor from *Science* who attended the meeting promptly followed up with an invitation to write a review article recapitulating the thrust of that presentation (Van Essen et al., 1992).

In 1987, Jack Gallant joined my lab at Caltech, having done visual psychophysics research as a graduate student but wanting to learn single-unit monkey neurophysiology. Inspired by a combination of psychophysical observations and computational considerations, Jack designed a family of "non-Cartesian" gratings and showed that many cells in area V4 responded better to rings, spirals, radial, or "hyperbolic" patterns than to conventional (Cartesian) sinusoidal gratings. This made for a colorful cover article in *Science* (Gallant et al., 1993), but more importantly provided insights relevant to how complex patterns and surface shapes are processed and perceived. These experiments were done in anesthetized monkeys, and Jack wanted to learn to train and record from alert monkeys. Soon after our move to Wash U (described below), Jack was inspired to head in a novel direction by examining neural responses during "free-viewing" (Gallant et al., 1998), an approach that he and others have followed up in subsequent years. On a personal note, Jack is the most irreverent (and at times acerbic) of those who I have mentored, and it made for many a lively conversation during his time in the lab.

After we moved to Wash U, Dan Marcus joined the lab in the mid-1990s and carried out an interesting project on how scene segmentation occurs in early visual areas. He showed that figures defined by featural contrast located well outside the classical receptive field elicited stronger responses than a simpler background stimulus and that this enhancement occurs in V1 as well as V2 but does not require visual attention (Marcus and Van Essen, 2002). While Dan showed talent and potential for neurophysiological research, his intellectual interests shifted, and he decided to switch fields after getting his PhD. He took a position in Randy Buckner's neuroimaging lab in the Psychology Department at Wash U. Dan designed and implemented a database to handle human neuroimaging data acquired by Randy's group and by other neuroimaging labs at Wash U and elsewhere. When Randy moved to Boston in 2005, Dan was persuaded to stay in St. Louis, join the Radiology Department faculty, and set up an independent

neuroinformatics endeavor. While I was pleased with Dan's decision for several reasons, I had no clue at the time how important his remaining at Wash U would become once the HCP came on the horizon.

Another project that I took a strong personal interest in was carried out by my student Xinmiao Peng. She found that many neurons in V1 and V2 respond to uniform illumination, but with a peak response to intermediate (gray) luminance rather than to the brightest (white) or darkest (black) stimuli (Peng and Van Essen, 2005). This ran counter to the conventional wisdom that V1 cells respond primarily to stimuli with spatial and/or color contrast within their receptive field. However, I had actually predicted the existence of "gray-preferring" cells on grounds that they would be computationally useful as a way to explicitly encode different shades of surface luminance. The inspiration for this prediction came from our efforts to implement algorithms for cortical segmentation, which occurred prior to Xinmiao's arrival but are covered in a later section.

The last of the visual neurophysiologists in my lab was Aki Anzai, a postdoc who studied form processing in area V2. The highlight of his project was the identification of cells in V2 having receptive field subregions that differed in their orientation selectivity (Anzai et al., 2007), consistent with earlier work by Jay Hegdé in my lab (Hegdé and Van Essen, 2003). Such cells are reminiscent of the "higher order hypercomplex" cells that Hubel and Wiesel (1965) had identified in cat extrastriate cortex more than 40 years earlier. I found it amusing and a tad ironic that the final visual neurophysiology project in my lab would resonate so strongly with work done by my postdoctoral mentors from decades past.

By the mid-2000s, I found that progressively more of my time and interests were devoted to the brain mapping and neuroinformatics efforts discussed below. Hence, I decided to phase out our visual neurophysiology and neuroanatomy lab and not to renew the NEI grant that had generously supported our research for three decades.

Before discussing our relocation to Wash U in St. Louis, a few additional comments about family life in Pasadena and California are in order. Pasadena was overall a good place to raise a family, though it was quite disappointing to find that the quality of the public school system had sunk far lower than what Isabel and I had experienced in our childhood, when California schools were ranked top in the nation. (We mainly blame the infamous statewide Proposition 13 that gutted school funding.) Isabel and I persevered in keeping our kids in public school, but she spent countless hours shuttling Scott and Brian to educational and other extracurricular activities that enriched their academic experience. Other highlights of family life included annual vacations in the Sierra Nevada Mountains. Our favorite spot was Lake Edison—a beautiful secluded lake that sadly is currently hardly more than a puddle owing to a severe drought. We started with tent camping when the kids were very young but soon graduated to annual

backpacking adventures. On one trip, we were lucky to survive because our Volvo's brakes nearly went out as we descended a steep downhill stretch near our destination. In a fleeting fast forward several decades, it was great fun to revisit the Lake Edison region recently with two of our grandkids (Jonathan and Anna) in tow (along with Brian and his wife LeAnn), at ages three and five, even earlier than when we had started with Brian and Scott.

The Transition to Washington University

Prelude

Several independent developments paved the way for my ending up at Wash U. The two most significant were my (unexpected) increasing engagement in administrative roles, plus a growing interest in human neuroimaging.

When I joined the Caltech faculty, I aspired to follow in the footsteps of my mentors by maintaining a strong hands-on engagement in experiments. I was able to put in full shifts on round-the-clock anesthetized monkey neurophysiology recordings that sometime lasted up to a full week. I also enjoyed being a scientific good citizen, such as serving on graduate admissions committees, but I was happy initially to steer clear of major administrative responsibilities. That changed unexpectedly in 1982 when I was asked by chairman Lee Hood to take up the role of Executive Officer for neurobiology, helping represent neurobiology faculty within the Division of Biology—a position that Jim Hudspeth had capably filled before deciding to step down. I accepted this responsibility with some hesitation and trepidation, and I certainly did not suspect it would prove to be a proverbial slippery slope that would carry me much farther down the road of many leadership roles (including the aforementioned role of CNS option representative, but many more to come).

Human neuroimaging. In about 1984, Mark Konishi organized a small conference at Caltech on cutting-edge systems neuroscience. One of the invited speakers was Marc Raichle from Wash U, who spoke about positron emission tomography (PET) imaging and showed early PET images of human visual cortex being activated by visual stimulation. John Allman and I immediately struck up conversations with Mark about using PET to map visuotopic organization in humans. This turned into a broader collaboration that also involved Peter Fox and Fran Miezen (Fox et al., 1986, 1987). It also planted a seed that not only fostered my interest in human neuroimaging, but also helped steer me toward Wash U some years later.

As a brief sidebar, another unsuccessful effort to predict the future involved musings about fMRI in the late 1980s, after MRI-based methods for imaging human brain structure had become commonplace. It was natural

to wonder whether some kind of MRI-based signal might somehow be used to image brain function. I recall a lunchtime conversation brainstorming on this issue at the Caltech faculty club with John Allman and Jack Richards (a father of nuclear magnetic resonance spectroscopy, which was a forerunner to MRI). However, our imaginations were too limited, as we keyed on phosphorus as the only potentially "useful" activity-dependent element (because it is in ATP), and we figured there just wasn't enough phosphorus around to provide decent spatial resolution. We missed the boat completely by not considering the fact that blood oxyhemoglobin and deoxyhemoglobin have different magnetic properties that might influence the vastly more numerous hydrogen atoms in water. Years later, I reviewed the first study that used fMRI to map human visual cortex (Belliveau et al., 1991). It became a cover article for *Science*, but while I was enthusiastic about the study, I didn't appreciate how it represented the tip of a large and rapidly growing fMRI iceberg.

Regarding Wash U, I had been aware that Gerry Fischbach had stepped down in 1990 as chair of the Anatomy and Neurobiology Department and that a search was under way for his successor. I knew that Lou Reichardt had turned down an offer of this position, and I subsequently heard my name mentioned in casual conversations as someone who might be considered for the position. I honestly gave it hardly a second thought until one day in the summer of 1991 when I received a call from Phil Stahl. Phil (who later became a good friend) introduced himself as a member of the search committee at Wash U and asked whether I would be interested in being considered for the chairmanship of the Anatomy and Neurobiology Department. I knew the department well, as it was Jim Kelly's old stomping grounds, and I had visited and given talks there several times over the years. Also, I knew several of the faculty at Wash U, including my former postdoc Andreas Burkhalter as well as the acting chair, Nigel Daw. I told Phil that I would consider it even though I felt well ensconced at Caltech and wasn't looking to move anywhere. I arranged to interview at Wash U right after the SfN meeting in New Orleans. As Isabel drove me to the airport for this trip, I recall saying it was rather unlikely that this would turn out to be an appealing opportunity. I was wrong. Partway through my interviews at Wash U, and literally while pausing for a moment on the bridge (over Euclid Avenue) that separated the preclinical and clinical portions of the medical campus, I had an internal phase transition. I suddenly not only realized that this was a great opportunity but that I really (gut to brain!!) wanted the position! I called the dean, Bill Peck, that evening to apprise him of my outlook. It took months for the search committee to make up its mind, but in late January 1992, Dean Peck called to say that Wash U would extend a formal offer. Isabel, Brian, and I visited in February, negotiated the specifics of the recruitment package, and looked at houses and school options for Brian. I accepted the offer officially in mid-March, circumventing

a protracted negotiation process. Within a month we made an offer on a house that we really liked, where we have lived for the past two decades.

Two factors loomed large in reaching a decision to accept the offer at Wash U. One was the appeal of helping strengthen a department that had a long tradition of excellence but had recently lost many excellent faculty. The second was a keen desire to expand my brain-mapping efforts into human neuroimaging in addition to the monkey-centric efforts we had pursued up to that point. Caltech at that time had no MRI facility and no human neuroimaging research, whereas Wash U had a strong neuroimaging program led by Marc Raichle and others, including Steve Petersen who I had known at Caltech.

We were keen to start in the fall of 1992, so that our younger son Brian could begin his junior year of high school in St. Louis. (Our older son Scott remained in Pasadena, as he had just finished his freshman year at Caltech.) To get my lab ready in time required fast-tracking a complex renovation effort. Lucille Miller, our departmental business manager, worked wonders to make this happen in record-breaking time. Lucille had very capably served the department (and with great devotion and loyalty) since Max Cowan hired her in the early 1970s, but this was the first of many times when I benefited from her administrative magic.

Research Centered at Wash U (1992—)

Fortunately, my entire group of postdocs and students at Caltech agreed to join in the eastward migration to St. Louis, thus allowing my lab to maintain momentum on ongoing projects, with only a short hiatus imposed by the move. Our visual neurophysiology efforts at Wash U were already described above. The next few sections cover the diverse topics of neural engineering (brief but important), neural development (including the part that started at Caltech), and our ongoing multifaceted efforts in cortical cartography and atlases.

Neural Engineering

One of my concerns when I decided to leave Caltech was that it would be difficult to maintain a long-distance collaboration with Charlie Anderson, given that his primary position was as an engineer at JPL. To my pleasant surprise, Charlie was enthusiastic about moving to St. Louis and transitioning to a full-time faculty position in the Department of Anatomy and Neurobiology. This became possible through sustained support from the McDonnell Center for Higher Brain Function.

Charlie's office was next to mine until he retired in 2008. We talked frequently and co-mentored a number of students and postdocs, including Subrata Rakshit and Brandon Westover. Over the next several years, Charlie

had deep conversations with other Wash U colleagues, including John Clark and Steve Highstein, and we (mostly Charlie) formulated a "systems engineering" approach that combines signal processing, motor control, and statistical inference. This provided a robust foundation for a theory of neural computation and a practical strategy for tackling specific computational problems. To support this project, we were fortunate to receive funding from the Mathers Foundation, a small private foundation based in New York. James Handelman, the foundation's scientific officer, was a colorful character who found personal enjoyment in supporting unconventional projects that included outside-the-box thinking, such as Charlie's theories.

As these ideas were gaining momentum, we were joined by Chris Eliasmith, a graduate student in the Philosophy, Neuroscience, and Psychology Program who had an unusual background that included interests in engineering, philosophy, and neuroscience. Chris was already a talented writer as well as a deep thinker. Chris and Charlie teamed up to write a seminal book *Neural Engineering* (Eliasmith and Anderson, 2003) that articulated an innovative general strategy for attacking problems in neural computation from a combined engineering and neurobiological perspective. It includes a framework (the Neural Engineering Framework, or NEF) that builds on and formalizes various approaches to population coding pioneered by Apostolos Georgopoulos, Bill Newsome, Tony Movshon, Mike Shadlen, and others. The NEF focuses on how neural systems compute and represent real-valued analog variables. This includes a robust mathematical framework for estimating how neuronal ensembles both encode and decode information at various levels, from sensory inputs, through higher-level "cognitive" abstract representations, to motor outputs that control behavior. Chris moved on to a faculty position at the University of Waterloo and has subsequently carried the flag through his modeling efforts there (e.g., Eliasmith et al., 2012).

Cortical Cartography, Part III: Caret, SumsDB, and Surface-Based Atlases

Our cartography efforts accelerated after the move to Wash U in 1992. A key starting point was when I recruited Heather Drury, who in the ensuing decade designed and implemented what became Caret (Computerized Anatomical Reconstruction and Editing Toolkit) software. In collaboration with Charlie Anderson, we developed a multiresolution approach to cortical flattening that was computationally efficient (Drury et al., 1996). In collaboration with Mike Miller in the Electrical Engineering Department, we developed methods for surface registration (Van Essen et al., 1998; see below). In 2001, Heather moved on, but I was fortunate to recruit John Harwell and Donna Dierker; their contributions over the subsequent decade allowed Caret to progress along many fronts (until we shifted to Connectome

Workbench, a new platform discussed later). Over the years, Caret became a workhorse tool in our lab and for thousands of other investigators for (a) surface reconstruction, visualization, and shape manipulation; (b) atlases and surface-based registration (SBR); (c) mapping parcellations and functional data onto atlas surfaces; and (d) interspecies comparisons between macaque and human cortex.

My grad student Jim Lewis was an early beneficiary of Caret's capability for reconstructing and flattening surfaces generated from postmortem histological sections and mapping experimental data onto the cortical surface. Jim used these tools to carry out a heroic set of analyses on the organization and connectivity of macaque parietal cortex (Lewis and Van Essen, 2000a, 2000b). This entailed parcellating the entire cerebral cortex using multiple architectonic stains and plotting the distribution of retrogradely labeled neurons following tracer injections into different cortical areas. This was along the lines of the approach pioneered by Joel Price, a good friend and colleague in our department who made seminal contributions to our understanding of orbitofrontal cortex (e.g., Carmichael and Price, 1994; Ongür et al., 2003). We were able to push the methodological envelope farther, by quantitatively mapping the distribution of retrogradely labeled neurons across the cortical sheet (Van Essen et al., 2001), thereby getting our foot in the door for the type of quantitative neuroanatomy I had long envisioned would be the wave of the future.

As it turned out, Jim was the last in the line of neuroanatomists in my lab who would carry out anatomical tracer-based experiments. It had become increasingly difficult to recruit students and postdocs and to obtain funding for "classical" neuroanatomy or even its modern computerized successors. I harkened back to conversations more than a decade earlier in which my neuroanatomical colleagues bemoaned the impending "death of neuroanatomy." Most vivid was a conversation on this topic with Leslie Ungerleider and Bob Desimone at the Caltech faculty club (Athenaeum). As I recall, my argument at the time was that neuroanatomy was simply much too important and fundamental, so it somehow would "find a way" to survive. But little did I realize how a host of stunning methodological advances would enable neuroanatomy to undergo a truly extraordinary resurgence, to the point where many erstwhile "pure" molecular and cellular neuroscientists have become dedicated neuroanatomical enthusiasts. (David Anderson at Caltech provides one of the most vivid examples on my radar screen.) In any event, my own involvement with quantitative tracer-based neuroanatomy entered a quiet phase, but it would reemerge about a decade later when I began a collaboration with Henry Kennedy's lab (see below).

MRI-based surface reconstructions. In the 1990s, it became routine to obtain high-quality structural MR images using conventional T1-weighted

scans. This motivated many successful efforts to implement segmentation algorithms that capture the shape of cortical convolutions in individual subjects (e.g., Dale and Sereno, 1993; Teo et al., 1997; MacDonald et al., 2000; Kriegeskorte and Goebel, 2001; Fischl et al., 2001; Han et al., 2004). Our contribution to this effort involved the SureFit (Surface Reconstruction by Filtering and Intensity Transformations) cortical segmentation algorithm. The basic idea underlying SureFit emerged from discussions I had with Charlie and Heather. The idea was to formulate image-processing algorithms that emulate the strategies used by the human visual system when we accurately (and usually effortlessly) determine what is or isn't cortical gray matter when inspecting a set of MRI slices. We came up with what I considered to be a clever set of strategies that in principle would be suited for a broad range of image segmentations applications (e.g., electron microscopic as well as MRI data). We decided (mostly at my urging) to patent the concept and the general method. We were successful in getting a patent, though it turned out to be quite an effort. Like most patents, the net result financially was a resounding zero in terms of commercial viability, but in any event, I take pride in this small feather in my cap. More important, Heather was able to implement SureFit initially into a free-standing application (Van Essen et al., 2001) that Donna Dierker later incorporated into Caret. It was widely used for a while, but never became totally automated. This became a serious limitation relative to competing methods such as the FreeSurfer method pioneered by Anders Dale, Marty Sereno, and Bruce Fischl (Fischl et al., 1999a, 1999b).

A distinctive feature of SureFit is that it generates segmentation and surfaces running along the cortical midthickness. This gives a representation of cortical surface area that is roughly proportional to the associated volume of cortical gray matter. Our emphasis on midthickness surface contrasts with other segmentation algorithms, including FreeSurfer, which generate surfaces running along the pial and/or white-matter boundaries. Fortunately, the midthickness surface can easily be obtained by averaging FreeSurfer white and pial surfaces once they are imported into Caret. It remains puzzling why a conceptually advantageous and simple-to-implement method hasn't been more routinely adopted, but I suspect it mainly reflects inertia, which is all too common even among scientists.

Beyond segmentation per se, the effort to implement SureFit yielded insights regarding information-processing strategies that work on real-world data, but I believe also have broader generality. One is to avoid premature "decisions" by throwing away information too hastily. Whenever experimental data (imaging or otherwise) is thresholded, subject to binarization, or smoothed spatially or temporally, then information is lost that might have been helpful. If a little bit of signal is buried in a lot of noise, there may be clever ways of extracting it if it hasn't yet been discarded. Hence, such steps should be postponed unless or until they are really necessary. Another

is to capitalize on transformations of data that make it more useful, on its own or when combined with other sources. For example, SureFit used a simple "intensity transformation" that made gray matter bright instead of gray (as it is in a T1-weighted scan). This was the step that generalized to Xinmiao Peng's characterization of "gray-preferring" cells in visual cortex described above.

Surface-based atlases. A major component of our brain-mapping efforts for the past two decades involves the generation, utilization, and sharing of surface-based atlases of cerebral and cerebellar cortex in multiple primate species—and even in rodents. The overarching perspective has been that atlases serve as an anatomical substrate for specifying where you are in the brain (by spatial location and in relation to functionally relevant areas, or parcels), and for comparing results across individuals and across studies. The importance of this idea has been generally appreciated in neuroimaging since the Talairach atlas was introduced as a book-based representation of stereotaxic coordinates and also of Brodmann cytoarchitectonic areas (Talairach and Tournoux, 1988). Also, Fox et al. (1985) promoted the use of stereotaxic coordinates for reporting activations in human PET imaging. Once MRI was on the scene, volume-based digital atlases were introduced, for example, the widely used MNI152 population-average atlas (Mazziotta et al., 1995). For cerebral cortex, I knew that surface-based atlases had much to offer, to enable mapping of data and subsequent analyses in ways that respect the topology of the cortical sheet. Some of these ideas were articulated in a "Solutions Are in the Surfaces" article in *PNAS* (Van Essen et al., 1998). We started down the computerized atlas road for macaque cortex using a histologically reconstructed individual surface (the "79–0" right hemisphere; Van Essen et al., 1998) and for human cortex using the Visible Man postmortem brain slices (Van Essen and Drury, 1997). Once high-quality MRI scans became available, we switched to the F99 atlas for the macaque and the Colin individual-subject atlas for humans (Van Essen, 2002a, 2002b). Among their advantages were the ability to represent subcortical data in volume slices as well as cortical data on surfaces.

Using a single subject as an atlas isn't a big problem for the macaque, because the folding patterns are relatively stereotyped. It's a major issue for human cortex, owing to the high degree of individual variability (Van Essen, 2004, 2005). Any individual human brain chosen as an atlas has intrinsic biases associated with the idiosyncrasies of its particular folding pattern.

As we emphasized early on (Van Essen et al., 1998), SBR is a critical part of the toolkit for multiple applications: (a) to register individual hemispheres to an atlas while respecting the topology of the convoluted cortical sheet, thereby preserving the spatial fidelity of data from each individual; (b) to enable generation of population average atlases that would

circumvent the biases of any individual subject; and (c) to enable interspecies registration that would open the door for exploring evolutionary expansion and homologies. As mentioned, we teamed up for a while with Mike Miller's group in Electrical Engineering, as he had mathematical expertise that complemented my lab's expertise in neuroanatomy and developing software tools. Our initial method was able to deform one cortical flatmap to another. However, this served mainly as a proof of concept and did not become a workhorse tool because it was difficult to arrange the cuts needed for flat-mapping to be in corresponding locations in an individual and an atlas. It was clear that SBR would be better done using spherical maps as source and target, as shown convincingly by Bruce Fischl and colleagues with their FreeSurfer software platform (Fischl et al., 1999b). While I was impressed by the FreeSurfer method, it wasn't directly translatable to some of the key needs associated with our lab's surface-based atlases. Once Mike Miller moved on to Johns Hopkins, we pushed forward on our own. John Harwell and I implemented a landmark-based SBR method (Van Essen et al., 2005). I then used this approach to generate a human population-average landmark- and surface-based (PALS) atlas (Van Essen, 2005) that was our primary atlas target for many years. It was eventually supplanted by the Conte69 atlas that did capitalize on FreeSurfer's SBR (Van Essen et al., 2012b).

Parcellations. Another role for surface-based atlases is to enable relating various types of data (neuroanatomical, neurophysiological, and neuroimaging) to cortical parcellations generated from other studies. For the macaque, we had relied for years on the Felleman and Van Essen 1991 (FVE91) parcellation, even though other competing parcellations provided alternative (and potentially more accurate) options. Once we had our hands on tools for SBR, we registered Jim Lewis's parcellations (and connectivity data) to a macaque atlas (Van Essen et al., 2001) and began an extended effort to bring other macaque parcellations under a common atlas umbrella (Van Essen, 2004; Van Essen et al., 2012a). For human cortex, fewer parcellations had been accurately mapped to cortical surfaces, but we later (Van Essen et al., 2012b) mapped many of them to an atlas surface that summarized the current state of the art. Our general conclusion at that time was that there was a long way to go before achieving a consensus parcellation in either species. To presage what will come later, the human cortex has finally leapfrogged that of the macaque in terms of having a comprehensive multimodal parcellation.

We were also able to generate surface-based atlases of the intensively studied mouse and rat cortex (Van Essen, 2002a; Van Essen et al., 2005), initially using histologically based atlas reconstructions (Paxinos et al., 2000; Paxinos and Franklin, 2012). These were followed by MRI-based

segmentations and surface-based atlases for both species. More recently, it has been very gratifying to see "ground truth" parcellations of mouse cortex emerge from the lab of my former postdoc, Andreas Burkhalter (Wang and Burkhalter, 2007; Wang et al., 2012) and also from the Allen Institute for Brain Science—though these have yet to be mapped to a surface-based atlas.

SumsDB. In anticipation that progressively more data would be mapped to our emerging family of surface-based atlases, I was also extremely keen to find better ways to share the data with the neuroscience community in a systematic but flexible way. In a nutshell, this called for a database that would be hospitable not only to data on surface and volume-based atlases but also on individual subjects. James Dickson joined the lab and worked with Heather and me to implement SumsDB (Surface Management System database; Dickson et al., 2001). This database was further refined by Ping Gu and has been populated by many diverse types of data, including more than 60,000 stereotaxic coordinate locations associated with nearly 2,000 studies, extracted from the literature and curated by Erin Reid in my lab. SumsDB is still widely used, but the uptake by the community in submitting their own data has unfortunately been less than I had envisioned. One lesson is that the process must be very user friendly for both submitting and accessing data in order to promote broad usage. To jump ahead for a moment, we are taking this to heart in our current efforts to implement a new database, BALSA (the Brain Analysis Library of Surface-based Atlases) by John Smith in my lab (http://balsa.wustl.edu).

Primate evolution and interspecies comparisons. Once we had surface-based atlases available for macaque and human cerebral cortex, it was of interest to see how they could inform our understanding of cortical evolution. Humans and macaques diverged about 20–25 million years ago (http://anthro.palomar.edu/primate/prim_8.htm) from a small, lissencephalic common ancestral primate (Allman, 1977). Our atlases confirmed that human cortex has 10-fold more surface area than a macaque (a 13-inch pizza versus a medium-sized cookie for each hemisphere; Van Essen et al., 2005). It was also known qualitatively that cortical expansion in the human lineage has been highly nonuniform, with greater expansion in regions implicated in higher cognitive functions, but it was difficult to pin this down with solid numbers. Using a set of candidate homologies based on various studies, we coaxed the landmark-based SBR method described above into successfully deforming the macaque cortex into registration with human cortex (Orban et al., 2004) and using this deformation to estimate that evolutionary expansion is around 30-fold in some portions of lateral temporal, parietal, and prefrontal cortex (Van Essen and Dierker, 2007) but as little as twofold in early sensory regions.

Because the great apes occupy a special niche as our closest living relatives, I was excited to access a single chimpanzee's MRI scans that enabled generation of a cortical surface reconstruction (Van Essen, 2006). More recently, Matt Glasser and I have been able to access a population of chimpanzee MR scans and to generate a population average atlas that includes myelin maps (Glasser et al., 2013b). Hence, even without access to fMRI or other modalities, the stage is set for evaluating interesting candidate homologies and systematically exploring differential cortical expansion across multiple primate species.

The cerebellum. While cerebral neocortex has dominated my scientific agenda, I have a special fascination with the cerebellum and also something of a "love-hate" relationship with it. I love the cerebellum for its beautiful organization at both a cellular level and at the macroscopic level of its accordion-like regular folds, compared to the more disorderly crumpling of the cerebral neocortex. The "hate" part (not really!) is because the cerebellar cortex has stubbornly resisted surface-based analyses to a frustrating degree. Its resistance to segmentation and surface reconstruction reflects the fact that it is very thin (about one-third that of typical neocortex) and has very little white matter underneath its graceful lobules and lamellae. Once I got access to high-resolution MRI scans for human, macaque, and rodents some years ago, I was keen to put SureFit through its paces in order to obtain the first cerebellar surface reconstructions. Alas, the initial segmentations were downright crummy. I persevered, spending hundreds of hours manually editing these segmentations (especially the human Colin cerebellum). Once reasonably faithful surface reconstructions were obtained, it was another arduous task to flatten the cerebellum, because it is essentially a very long and skinny sheet with internal irregularities that were resistant to "well-behaved" flattening. Finally, they yielded, and I was very pleased to report on human, macaque, rat, and mouse cerebellar surfaces (Van Essen, 2002b) and to make them part of our freely available atlas suite available via SumsDB. Recently, Marty Sereno has generated a higher-quality human cerebellar segmentation using a postmortem MRI scan; it shows about twice the surface area of the Colin cerebellum that I segmented. However, it is inadequate for many purposes to have just an atlas cerebellar surface based on a single individual. If anyone finds a way to robustly and automatically generate cerebellar segmentations and surface reconstructions from high-quality in vivo structural MRI scans (e.g., the HCP data discussed below), it will open up a fascinating arena of exploration of a still-mysterious major brain structure.

Neural Development

My involvement in neural development extends over four decades and involves three broad directions: synapse elimination, cortical development,

and a theory of tension-based morphogenesis. Our efforts on synapse elimination were carried out entirely at Caltech, but the discussion was postponed until this section in the interests of thematic continuity.

My fascination with neuromuscular synapse elimination started serendipitously in Norway, then continued for many years in the capable hands of a succession of Caltech graduate students—John Bixby, Herman Gordon, Ed Callaway, Karina Schimmerling-Cramer, and Jim Soha. Our initial work in Oslo had used rats, but John and I decided to introduce rabbits as a model system that proved to have several advantages, including larger size at birth (Bixby and Van Essen, 1979). Herman Gordon followed up on this by analyzing the maturation of fast-contracting versus slow-contracting muscle fiber types within the rabbit soleus muscle. He showed that motor neurons innervate the different fiber types with high specificity even during the period of extensive multiple innervation (Gordon and Van Essen, 1985). Ed Callaway carried out what to me is the most intriguing of our neuromuscular projects, using selective inactivation of axons by inserting tiny tetrodotoxin-laden silocone plugs into one of the two segmental spinal nerves supplying the soleus muscle. The results demonstrated a clear advantage of inactive synapses when competing against active ones (Callaway et al., 1988, 1989). This "anti-Hebbian" synaptic competition seemed initially very counterintuitive, as we had long been attuned to singing the Hebbian mantra of "neurons that fire together wire together." However, the results actually made a lot of sense functionally when considering the motor unit size principle, which states that smaller motor units are recruited more readily during reflex behaviors, and thus are presumably more active overall (Henneman et al., 1965). This would be a natural outcome if synapses from less active neurons are at a competitive advantage. Anti-Hebbian synaptic plasticity has been reported in other contexts and systems (e.g., cerebellar spike-timing-dependent plasticity; Roberts and Leen, 2010), but whether this is mechanistically related to what Ed and I reported remains to be determined.

When I launched parallel research projects on visual cortex and neuromuscular development at Caltech, I had hoped that there might be an eventual convergence or cross-talk, perhaps in the realm of studying synaptic plasticity in visual cortex. However, I admit to not having a focused vision or game plan for taking our research in such a direction. In the end, a felicitous convergence arose from a project on the development of cortical connections, which Tom Coogan started when he arrived as a postdoc at Caltech.

Tom had gotten his PhD with Andreas Burkhalter at Wash U studying hierarchical organization of rat visual cortex, but he was interested in the development of cortical connections. He was delighted by the opportunity to return to St. Louis and Wash U. We decided to explore the development of macaque cortico-cortical connectivity using as a tracer a lipophilic dye ("diI") that slowly diffused along axons when placed as focal deposits in

postmortem brains. Among the various interesting observations was the finding that bidirectional connections between V1 and V2 are established during the period of prenatal development when cortical folding starts to occur (Coogan and Van Essen, 1996). That key observation leads directly into the next story.

An "Aha" Moment

Discovery is at the heart of why science is fun as well as exciting, but it plays out in many ways. Often discoveries come slowly, emerging only after a hard-fought battle to acquire, analyze, and interpret data of one sort or another. Occasionally there are true "aha!" or "light-bulb" moments. My absolute favorite light-bulb scientific moment of my own career came in 1996. I was sitting on our living room couch musing about anatomical connectivity patterns in visual cortex. I started by considering several facts that I had not previously conjoined: (a) areas V1 and V2 are powerfully interconnected by visuotopically organized projections; (b) in the macaque, cortical folding brings V1 and V2 opposite one another, making the distance between topographically corresponding locations relatively short; and (c) as Tom and I had just shown, interareal connections are established right around the time that cortical folding begins. It suddenly dawned on me that there might be a causal relationship. If axons happened to generate mechanical tension as they establish interareal connections, then regions that are strongly connected might be pulled closer together by virtue of a coordinated action of millions of tiny "fishing lines" being reeled in by the neuronal cell bodies ("fishermen") benefiting from intercellular adhesion by synaptic contacts at the distant end. By this hypothesis, a gyrus would form in between the strongly connected regions (a winner), whereas a sulcus would represent the outcome of a losing battle in which weakly interconnected regions would become separated by a longer distance within white matter.

I quickly became excited (and obsessed) with this idea, because it was appealingly simple, yet had potentially broad explanatory power. If this idea could explain what was happening between V1 and V2, surely it might be relevant to the rest of cerebral cortex. Two further issues sprang to mind: (a) Was there any evidence that axons actually do generate mechanical tension? (b) Who else had proposed this idea and (gulp) published it previously, since it now seemed very obvious. For all I knew it might have been proposed by one of the great neuroanatomists or developmental biologists anytime between the present and the preceding century.

I had informative conversations with several colleagues at Wash U, including Josh Sanes, Jeff Lichtman, and Paul Bridgman, who helped shape my early thinking and point to relevant literature. I had vaguely recalled an earlier study by Dennis Bray inferring that neurites in tissue culture indeed generate tension. Then I learned about beautiful studies by Steve Heidemann

and colleagues at Michigan State, showing that chick sensory neurons actually do generate a hefty amount of tension—plenty to drive morphogenesis (Lamoureux et al., 1989, 1992). The Heidemann lab later reported that explanted chick forebrain neurons generate much less tension than the spinal sensory neurons (Chada et al., 1997). I might have taken this as the death knell of tension-based cortical folding, but I decided there are any number of reasons why cortical neurons in a dish might not "feel like" generating much tension under particular experimental circumstances. For a broader context I devoured the wonderful book *On Growth and Form* by D'Arcy Thompson (1921). He thought deeply about how competing forces of tension and pressure shape all things biological. Had he been interested in the brain, I strongly suspect he would have proposed tension-based morphogenesis himself.

A strongly appealing aspect of tension-based morphogenesis is that wiring length minimization in a sense comes along, free for the ride. If every axon and dendrite is pulling, then the tendency is for wires to become shorter, and they will tend to be shortest of all when many axons are pulling together. "Compact wiring" is profoundly important in electronics (computer chip makers invest billions of dollars in this). Others (e.g., Mitchison, 1991) had proposed that neuronal components are placed so as to minimize wiring length, for example, in terms of position within a 2D cortical sheet (Cherniak, 1995).

With a lot of help from my friends, I wrote a manuscript on the tension-based morphogenesis hypothesis and eagerly submitted it to *Science*. In relatively short order, I received an editorial rejection from the editors—they did not even see fit to send it for review. Infuriated, I contacted a senior editor and pleaded my case, but got absolutely nowhere. I have received my share of manuscript rejections, both before and after this episode. In general, I have tried to be philosophical and roll with the punches in such situations, but this one really got my goat. Chastened but not defeated, I revised the manuscript and submitted it to *Nature*, where it fared much better after a constructive round of reviews. It has become a widely cited publication, and to this day it routinely elicits interest if not outright fascination when I mention tension-based cortical folding in talks and seminars, even if only briefly.

As appealing as tension-based morphogenesis was and is, I have studiously avoided the temptation to assume that it *is* true just because I and others like the idea and want it to be true. There are a few studies providing strong evidence that this is unlikely to be the full story, insofar as differential proliferation may contribute to primary gyral formation in some regions (Reillo et al., 2011). What I find notable, but also ironic and frustrating, is the number of studies that have reported the demise of tension-based morphogenesis based on evidence or logic that I personally find tenuous or shaky (Xu et al., 2010; Nie et al., 2012; Bayly et al., 2013). This is not the place to delve into the details. What I can say (and indeed have often said) is that if a sealed envelope containing the "definitive" answer were

placed in front of me, I would unhesitatingly wager large sums that tension-based morphogenesis is a dominant contributor to cerebral cortical folding. Moreover, it can account for other phenomena in neural development. For example, why is the cortex a sheet-like tissue, even in lissencephalic brains, whereas subcortical nuclei tend to be irregular blobs? My straightforward explanation is that the cortex is dominated by cellular structures with a radial bias (apical dendrites of pyramidal cells plus radial glial processes), and tension along such processes would tend to keep the cortex thin even as it expands in volume and therefore surface area; in contrast, subcortical neurons tend to have more isotropic dendrites, and therefore expand more uniformly in all directions. Mechanical tension can also explain why the retina has a fovea (in species where it does), and some (but probably not all) aspects of the radically different nature of how the cerebellum gets its folds.

Human cortical maturation. My involvement with human cortical development began in 2005 when a first-year medical student, Mai-Lan Ho, approached me about doing a summer project related to human cortical development. I had not previously worked in this arena, but I told her that there might be an opportunity because I had recently encountered a paper by Bob McKinstry, Jeff Neil, and colleagues (McKinstry et al., 2002) in which they showed high-quality in vivo structural MRI scans of neonatal human brains. Since Bob and Jeff were both at Wash U, I arranged to meet with them and explore a possible collaboration. They were enthusiastic, and they also apprised me that they would soon be joined by another pediatric neuroimager, Terrie Inder, who had just been recruited from Australia to join the Wash U Pediatrics Department to lead an effort in neuroimaging of preterm infants. Terrie, Jeff, and I hit it off both scientifically and personally. We began a collaboration that continued until 2013 when Terrie and Jeff were recruited to Boston. It was my first direct involvement in a clinically relevant project, as premature birth is associated with a host of later developmental disorders. I still recall Terrie giving me a personal tour through the Neonatal Intensive Care Unit (NICU) at Children's Hospital. Isabel and I became good friends with Terrie and Jeff (who were together at the time and were married a few years later) and recall many enjoyable social events at their house.

Jason Hill was the first graduate student Terrie, Jeff, and I jointly comentored. Jason worked with an engineering student, Andy Knutsen, to implement a semi-automated cortical segmentation algorithm (LIGASE) that worked reasonably well on perinatal brains despite the dramatic age differences in tissue contrast as seen in T1-weighted and T2-weighted scans. Jason then used this to characterize cortical morphometry (folding patterns) in neonatal as well as preterm infants. The finding I found most intriguing is that neonatal cortex is on average one-third the surface area as

in adults, but the expansion occurs nonuniformly, with regions we associate with higher cognitive functions (lateral temporal, parietal, and prefrontal cortex) expanding about twice as much as early sensory and motor regions (Hill et al., 2010). This ties in nicely with other aspects of cortical nonuniformity, including evolutionary expansion (see above), myelin content (Glasser et al., 2013), and dendritic arbor size (Elston and DeFelipe, 2002).

Leadership Activities

With the notable exception of my desire to take the chairmanship position at Wash U, I have in general not sought out leadership positions that have come my way. If I have my druthers on any given day, I would rather work on matters of science than administration. Nonetheless, over the years, numerous opportunities or requests have been proferred. I have often said yes, if I think (a) my efforts will make a difference for the better and (b) I can preserve enough time in the day to remain heavily and directly involved in ongoing research projects in the lab. As events have played out, the outcomes have generally been positive on balance—that is, I can look back and say that I'm glad I did it (and usually glad when it's over!). The next few subsections provide a personal perspective on some of these leadership activities. Near the end, I will offer a brief perspective on some of the lessons learned.

It was a privilege to serve as chair (officially called the head) of the Anatomy and Neurobiology Department at Wash U for 20 years—almost half as long as the 42 years served by Robert Terry, the founding chair of the Anatomy Department. Max Cowan (chair from 1968 to 1980) brought the department into the modern neuroscience era, recruiting a number of outstanding neuroanatomists. Gerry Fischbach (chair from 1981 to 1990) recruited many cellular and molecular neuroscientists. From a faculty recruitment perspective, my objective was to strengthen the department broadly, including systems, cellular, molecular, and developmental neuroscience. This was one of the more rewarding facets of the position. We started with recruitments in cellular, molecular, and developmental neuroscience. This was in part to send a clear message to the department of my intent to maintain its breadth. It also reflected a practical constraint, which was that I wanted to recruit systems neuroscientists working on nonhuman primates, but this wasn't logistically feasible until completion of a specialized primate facility in the new East McDonnell building that was part of my recruitment package.

Retention of key faculty was a more challenging aspect of the job. We were successful in many cases (including two rounds with Josh Sanes and Jeff Lichtman) but certainly not all cases over the years. Losing stars like Sanes and Lichtman to Harvard and Rachel Wong to the University of Washington despite intensive retention efforts was among the most disheartening aspects of the job. Nonetheless, this is part of the competitive

nature of academia, and it even had its eventual upsides insofar as we were subsequently successful in recruiting fresh junior faculty who have been highly successful (e.g., Tim Holy, Valeria Cavalli, Paul Shaw, Camillo Padoa-Schioppa, and others). The Executive Faculty system at Wash U also entails numerous responsibilities for the Medical School and the university more broadly. These were often challenging and generally rewarding. However, at the end of two decades and countless committees, I was delighted to hand over the reins to my successor, Azad Bonni, and to wish him the best in keeping the department on a forward trajectory. My loyal administrative assistant, Susan Danker, has remained on board, helping me with countless organizational matters and making my life more efficient and enjoyable since she began working with me in 1992.

I was also interested in promoting interactions across disciplines and between the medical school and Danforth (Hilltop) campuses. This included service on numerous search committees, including the chairs of psychology (Roddy Roediger), biomedical engineering (Frank Yin), and biology (Ralph Quatrano). Energizing the psychology and biomedical engineering programs in turn helped in the later launching of the interdisciplinary Cognitive, Computational, and Systems Neuroscience graduate pathway that continues to prosper. Another unique opportunity was to serve on the search committee for the Wash U chancellor, after Bill Danforth (one of my heroes and a true gentleman and farsighted leader) decided to step down in 1995. For one of the initial interviews, four of us were flown on a private jet (available to one of the trustees) to meet with a candidate in Boston. I was impressed by the clarity of thinking and speaking by this candidate, Mark Wrighton, who was offered the position and has served with distinction for nearly two decades at the time of this writing.

The Wash U neuroscience community has benefited enormously from the two endowments specific to neuroscience and devoted to their programmatic enhancement. The story of how the McDonnell Center for Higher Brain Function (now the McDonnell Center for Systems Neuroscience) came into existence in 1980 is fascinating and also instructive about the myriad interactions between scientists, donors (James S. McDonnell), and institutional leaders. Robert Grubb's history of the Wash U Neurosurgery Department includes a very entertaining rendition of this story (Grubb, 2011). I enjoyed serving as director of this Center for more than a decade, working closely with Dennis Choi, and later Chuck Zorumski, who were directors of the McDonnell Center for Cellular and Molecular Neuroscience, established in 1983 and initially directed by Gerry Fischbach.

Neuroinformatics, the Human Brain Project, INCF, and NIF

Between 1989 and 1991, I served on a Committee on a National Neural Circuitry Database organized by the Institute of Medicine and chaired by

Joe Martin (then at UCSF). The committee's report articulated a vision for neuroinformatics (though it may not have used the term) that had a far-reaching impact. It laid the groundwork for the original Human Brain Project (HBP), a decade-long effort launched in 1993 to promote brain mapping and the nascent field of neuroinformatics. (It is not to be confused with the current European Human Brain Project, which is completely different in scale, style, and geographic center.) Led by visionaries Steve Koslow and Mike Huerta, the original HBP didn't have a budget, but it was nonetheless able to fund many grants by soliciting support from various federal agencies, including NIH, NSF, Department of Energy, and Department of Defense (Huerta et al., 1993). I received an HBP grant (now in its 21st year) that was critical for expanding and sustaining my lab's brain-mapping efforts. The HBP held annual meetings on the NIH campus that served to catalyze and coordinate efforts. While these meetings helped build a sense of community, a frustrating aspect for some of us was that we were mostly preaching to the converted and was not (yet) successful in strongly engaging the broader neuroscience community. That would change, but not quickly. In 2005, the HBP was phased out as a distinct program, having successfully served a catalytic role for more than a decade.

In the mid-1990s Steve Koslow also catalyzed an international effort via the Mega Science Forum to promote coordination of brain mapping, informatics, and databasing. In serving on this committee for a couple of years, one of my recollections is that way too much time was spent repeatedly debating whether to use a broad definition of neuroinformatics (which encompassed computational neuroscience) as favored by the Europeans, or a narrower definition (which emphasized just the databasing aspects) as favored by some of the U.S. representatives. In the end, the broader definition prevailed, which I felt was a more sensible outcome. The report of this committee led to the establishment of yet another committee(!), which eventually (in 2005) led to the establishment of the International Neuroinformatics Coordinating Facility (INCF). The INCF has its home base in Stockholm but has a broad international reach. I enjoyed serving on several of the INCF working groups, which aim to promote greater coordination and cooperation in the informatics domain.

Another neuroinformatics-related endeavor that emerged over the past decade is the Neuroscience Information Framework (NIF). NIF (https://neuinfo.org) is a web-based portal that provides rapid access to a large fraction of the amazingly diverse online resources associated with neuroscience. The NIF project was catalyzed by the Brain Information Group mentioned in the next section, which captured the attention of the NIH Blueprint for Neuroscience Research (http://neuroscienceblueprint.nih.gov). I was closely involved in the early days of getting the NIF project funded and under way, which had some touch-and-go moments. The many other neuroscientists, neuroinformaticians, and NIH leaders who helped in this endeavor are

too numerous to list individually, but I think it is appropriate to identify Maryann Martone at UC San Diego as the project leader, who made particularly seminal contributions to the success of the NIF. There are some entertaining aspects to the NIF story, and hopefully a more complete history will emerge in due course.

Journal of Neuroscience *and Society for Neuroscience*

My extended period of involvement with various aspects of the SfN started innocently enough around 1990 when Dale Purves, then editor in chief of the *Journal of Neuroscience*, invited me to join the editorial board for the journal. Dale stepped down in 1993, and things did not go smoothly for his successor. One day in May 1994, I received a telephone call from Larry Squire (SfN president at the time) asking whether I would be willing to consider stepping up to the plate and serve as editor in chief for the journal. I told Larry that my platter was more than full, and I encouraged him to skip me and proceed to others on his short list. Larry apprised me that I was already the last person on his short list, and that if I declined, their committee would be back at square one! He also said it was urgent that I decide within just a few days. After deliberating and consulting with Isabel and a few others, including Jeff Lichtman, I decided to take the position. The transition took place very quickly. We implemented many changes to improve the timeliness and rigor of the review and decision process and to communicate to the neuroscience community a commitment to a fast and fair review process. Fortunately, submissions to the journal more than doubled in my four and a half years in this role, before I decided that one term was enough and gladly handed the reins over to my successor, Gordon Shepherd. However, it was not entirely smooth sailing. An effort that proved ahead of its time involved the launching of "Rapid Communications," an all-electronic version of the journal that aimed to attract brief but high-profile articles. This did not catch fire with prospective authors, and "Rapid Communications" soon reverted to printed "Brief Communications." Of course, printed journals are now largely historical relics—what a difference a couple of decades makes!

In 1999, I was elected to a four-year stint on the SfN Council. This was a very interesting experience, especially with the transition to the new executive director, Marty Saggese, who encouraged a thoughtful long-range planning process. A few years later (in 2002), I was elected SfN Secretary, which had traditionally been a pro forma job with no substantial duties other than serving on Council. However, the preceding Council had decided to give the secretary a "real job" by also chairing a newly established Committee on Committees. This committee's task was to identify who would serve on and chair the many different SfN committees (a task previously handled by Council, sometimes with insufficient time to deliberate).

When Huda Akil became SfN president in 2003, she expressed a strong interest in neuroinformatics as a domain of growing importance to the neuroscience community. For her presidential initiative she set up an ad hoc Brain Information Group (BIG), which I was delighted to serve on. The report of the BIG committee led to establishment of a standing Neuroinformatics Committee for the SfN. It also helped catalyze the NIF project described in the preceding section. I think the Neuroinformatics Committee played a valuable role during its five-year existence, but it struggled to articulate a vision and a plan that consistently resonated with the SfN Council in subsequent years (despite concerted efforts from me and others).

In 2005, I became SfN president-elect, and in 2006 served as president. It was interesting and rewarding in many respects, as there was an opportunity to help shape many of the Society's activities. For the "Dialogues in Neuroscience" public lecture series, I selected Jeff Hawkins of Palm Pilot fame, who had thought very seriously about the brain and computational neuroscience and had written a thought provoking book, *On Intelligence* (Hawkins, 2004). His presentation at the SfN meeting was well received, as were the four presidential lectures by distinguished investigators that I had invited in the areas of neuroinformatics and computational neuroscience. All was not hunky-dory, however, as Council decided over my objections to phase out the Neuroinformatics Committee. I was disappointed and felt that the decision lacked foresight. Nonetheless, it has turned out that neuroinformatics has continued to prosper as a subfield of growing importance and recognition. In 2007, I came to the end of a 14-year period in which I had more or less continuously been associated with a major SfN leadership role. It was a great ride overall, and I'm happy to be added to the ranks of SfN past presidents!

Organization for Human Brain Mapping

In the early 1990s, I attended annual BrainMap meetings in San Antonio that were organized by Peter Fox. The meeting grew in size as neuroimaging gained in popularity, but it was by invitation rather than an open meeting. At the 1994 meeting, there were conversations about a public human brain-mapping meeting, which Bernard Mazoyer had volunteered to organize in Paris the following June. I was invited to be a keynote speaker at the first meeting. This surprised me because I was a monkey cartographer and hadn't yet delved directly into human brain mapping. Per Roland, one of the organizers, explained that they wanted at the outset to build a bridge to the community of nonhuman primate investigators rather than focusing exclusively on human neuroimaging. The meeting in Paris was a great success, with about 600 attendees. Jack Belliveau and colleagues stepped up and volunteered to host a meeting in Boston the following year. However, it was also evident that some organizational structure was needed in order to

provide continuity and sustainability for having regular annual meetings. But how to bootstrap from nothing to something? At the next BrainMap meeting in San Antonio (December 1995), a group of us self-assembled into an ad hoc committee who tasked ourselves with drafting a set of proposed bylaws for a human brain-mapping entity. Most of the effort was straightforward, but a contentious issue arose regarding whether this should become an "organization" that would focus exclusively on organizing an annual meeting, or a "society" that might feel empowered to undertake a broader set of potential activities and responsibilities. The issue was put to a vote at a town hall meeting held at the Boston meeting. There were strong advocates on both sides. Our ad hoc committee had selected Alan Evans to chair this discussion, and I recall him wearing an army helmet in mock fright at the flack he might take as our committee sat on stage. In the end, the Society for Human Brain Mapping (SHBM; pronounced ShhhBoom) was voted down, and the more mundanely named Organization for Human Brain Mapping (OHBM) was officially launched.

At this town hall meeting, there was an election for a council that would steer the nascent organization. I was on the slate of candidates, and perhaps because I had been relatively vocal during the town hall discussion, I was elected to the first council. One of the action items at the first council meeting was to elect a chair. Two of the newly elected councilors were obvious candidates to become chair because each was an editor of a leading neuroimaging journal. Informal hallway conversations prior to the meeting made it clear that the council was strongly and approximately evenly divided. One of the new councilors, Bruce Rosen, suggested that the council identify a compromise candidate not associated with either "camp." He asked me whether I would be willing to serve in such a role. Once again, with precious little time to ruminate, I agreed to take on this role, thereby becoming the founding chair of the OHBM council. It has been highly gratifying to see the OHBM prosper and become the leading "go-to" conference for a large portion of the neuroimaging community.

Allen Institute for Brain Science

I previously mentioned a couple of examples of philanthropic benefactors (Arnold Beckman, James McDonnell) whose generosity to neuroscience had an important, albeit indirect, impact on my career. In recent years I have had the privilege of serving on advisory boards for the Allen Institute for Brain Science, a private institute in Seattle funded through the generosity and vision of Paul Allen, the cofounder of Microsoft. The Allen Institute was launched in 2003 to tackle major problems in neuroscience that could be better handled by an industrial-scale operation than by conventionally funded neuroscience labs. The institute started with a mouse gene expression atlas and then expanded to include many other large-scale projects

relating mostly to mouse and human brains. It has benefited from exceptionally strong leadership, including Allen Jones (a Wash U alum) and more recently, Christof Koch (whom I helped recruit to Caltech two decades earlier!). I joined the Human Brain Atlas Advisory Council in 2007 and the Scientific Advisory Board in 2010, becoming its chair in 2013. In exchange for providing (hopefully) useful high-level advice to the Allen Institute, board members get to learn about the latest progress in cutting-edge neuroscience and technology. For me, there has been a personal benefit as well, because multiple visits per year to Seattle have made it easier to visit family living in the area—initially Brian and family when he was a computer science graduate student at the University of Washington, and now Scott and family (wife Myra and grandkids Laurel and Max) since he took a job in the area.

Lessons Learned

Before proceeding to the final major story in this chapter, I will offer (at the behest of a colleague who read an earlier draft) reflections on approaches that may have helped in the success of various leadership activities. Here are a few. They are by no means novel, but perhaps they provide a useful perspective.

- *Listen!* I think it's extremely important for leaders to listen more than talk. And when listening, try to understand not only the words but also the subtext and the underlying intent of what others are trying to say.
- *Balance!* Leadership is tested when dealing with differences of opinion. A good starting point is to strive for balance, seeing both sides of the debate, and looking for compromise solutions when that makes sense.
- *Go to the mat rarely.* When tough problems arise and critical decisions need to be made, it is sometimes necessary to draw a line in the sand and/or make a stand on principle and against objections. I have intentionally avoided discussing most of the contentious and sometimes thorny problems faced over the years (though there have been enough to fill another chapter!). Overall, I feel it's important to choose battles carefully, avoiding them when possible because they can be emotionally draining and enormous time sinks.
- *Keep an even keel.* The hot temper I mentioned having as a child has mellowed for the most part, for which I am grateful. It is sometimes appropriate and useful to express anger, but in my experience, it is usually much better to keep emotions in check.

The Human Connectome Project

My role in the HCP emerged via a cascade of numerous serendipitous events. Given the uniqueness of my involvement, I will describe the early parts of this story at some length, to provide a personal perspective on a scientifically important endeavor. A key early event in redirecting part of my research effort was in May 2008, when I received an e-mail from a prospective student, Matt Glasser, who had been offered admission to the Wash U Medical Scientist Training Program (MD/PhD) program. Matt had extensive prior experience with neuroimaging of humans and nonhuman primates while a student and then a research assistant at Emory University, and he had clear notions regarding two projects he was interested in working on. One was a novel approach to estimating cortical myelin content using structural MRI scans, based on preliminary observations he had made at Emory. The other was to examine anatomical connectivity using diffusion imaging and tractography. I didn't have direct experience in either of these realms, nor did I have imaging data to fuel either project. What I could offer was expertise in neuroanatomy and in the surface-based analyses that we both agreed was vital for both projects. I was also willing to go out on a limb, especially since I had been impressed when interviewing Matt earlier that winter. Matt accepted and began a rotation in my lab in the summer of 2008. He hit the ground running, as he had access to structural and diffusion imaging data from macaques, chimpanzees, and humans via a continuing collaboration with Todd Preuss and Jim Rilling at Emory. On the myelin-mapping front, Matt was able to generate promising myelin maps based on T1-weighted/T2-weighted ratio in all three species. On the tractography front, I saw one of my roles as playing devil's advocate, challenging Matt to find compelling evidence for major pathways such as between V1 and V2, where ground truth was known. (The tractography versus tracer comparison has also finally come to fruition, but it took much longer and also engaged another MSTP student, Chad Donahue.)

Another important event got under way later that summer, when Walter Schneider from the University of Pittsburgh called and asked me to join an advisory board for a forthcoming Brain Competition 09. This was an event he had organized for several years running, with a different theme each year. For the 2009 competition, Walt had decided presciently to focus on mapping the human connectome. The advisory board was asked to provide guidance on data acquisition parameters that would be optimized to allow competitors to parcellate the cortex using structural connectivity (diffusion imaging plus tractography) and resting-state functional connectivity (rfMRI). My expertise was on cortical anatomy and parcellation, and when the teleconferences turned to neuroimaging data acquisition parameters, I found myself still in the early stages of a steep but invaluable learning curve on various nuts-and-bolts issues of MRI data acquisition. My role was in large part to emphasize the lack of ground truth and the critical

issues involved in parcellation of human cortex. Walt was a true visionary in promoting this endeavor, but I also considered him wildly optimistic in terms of what the methods at the time would be able to deliver in terms of parcellating cortical areas and charting connectivity.

It took months for the advisory panel to settle on the data acquisition parameters and for Walt's team to acquire and share the data. We eventually settled on ground rules for judging the competition and formally announced the competition the spring of 2009. In the meantime, Alex Cohen in Steve Petersen's lab was developing a novel approach to cortical parcellation based on spatial transitions in functional connectivity. Alex was using our Caret software as part of his analysis, and I was part of this collaborative effort (Cohen et al., 2008) as well as a member of Alex's thesis committee. As word got out about the forthcoming competition, Alex, Matt, and another MSTP student, Tim Laumann, decided to go in as a team (after we were assured by Walt that it was not a conflict of interest for students of advisory committee members to enter the competition). They got a head start in methods development based on Alex's efforts as well as innovative approaches and ideas generated by Matt and Tim. They applied the novel multimodal parcellation method that emerged to the competition's publicly released data set and submitted their analysis by the deadline before the June 2009 meeting of the OHBM. Alex, Matt, and Tim emerged as co-winners of the competition, but nobody involved was under the illusion that an even remotely accurate cortical parcellation had been achieved. It was an important lesson for everyone about the complexity of the challenge.

Meanwhile, an even more important and potentially exciting opportunity loomed on the horizon. It is a long saga that is still playing out. Here I focus mainly on the early stages of the process and from a personal standpoint. It started in early May 2009, when Mike Huerta (whom I knew well from neuroinformatics efforts described above) sent out a heads-up e-mail that I and many other neuroimagers received, indicating that NIH intended to launch the HCP by awarding a $30 million, five-year grant to study human brain connectivity in "up to several hundred" healthy young adults. I read the e-mail with modest interest but mentally tucked it away as something I was unlikely to get actively involved in. Later that month, in an informal conversation right after a meeting of Alex Cohen's thesis committee, Marc Raichle mentioned this e-mail, as it had been sent to him and to the other two committee members, Steve Petersen and Brad Schlaggar. We discussed whether Wash U should consider throwing our collective hat in the ring. Mixed feelings were expressed, but we all agreed that this was worth further consideration. To initiate follow-up discussions, I agreed to convene a meeting of key local stakeholders. At the first meeting, someone suggested that it would be pretty cool to study brain connectivity in identical twins (to enable analyses of the heritability of brain circuits) and also noted that Andrew Heath in the Psychiatry Department had a long track

record in studying twins in projects relating to addiction. With encouragement from Chuck Zorumski, chair of psychiatry, we approached Andrew, who was immediately enthusiastic even though he had not previously been involved in neuroimaging studies. Thus, the wheels started turning a bit faster.

It was obvious that a project of this scope would entail partnering with investigators at other institutions who could add strength in domains where Wash U was "underpowered" (e.g., MR physics, diffusion imaging, and magnetoencephalography, or MEG). I became the informal de facto point person representing Wash U as we entered a "courtship dance" with various potential partners. Two important conversations took place at the OHBM meeting in San Francisco. I met with Tim Behrens, whom I had gotten to know from our involvement in the Pittsburgh Brain Competition advisory group, and who had interacted a lot with Matt regarding tractography methodology (and also through his collaboration with Jim Rilling, Matt's former research mentor at Emory). Tim was enthusiastic about a possible partnership, but his close colleague at Oxford, Steve Smith, was provisionally aligned with another nascent consortium. Also at the OHBM meeting, I was approached by David Feinberg, an MR physicist who had previously been at Wash U. David expressed interest in a possible partnership and encouraged me to consider others, including Kamil Ugurbil at the University of Minnesota (U Minn). I was impressed when I heard Kamil give a talk at the same OHBM meeting, but our first face-to-face meeting didn't occur until later that summer.

In the meantime, we continued various exploratory conversations. For a while it appeared that a partnership with the team at Massachusetts General Hospital (MGH) might work out, but that didn't happen for various reasons. Once the formal request for applications was announced in mid-July, we had a better idea of what would need to be pulled together—and quickly, because the due date was in November, just a few months down the road. We soon decided to explore the U Minn opportunity more seriously. In early August, I e-mailed Kamil, who was in Europe at the time, but we jointly rolled up sleeves immediately on his return. By mid-August, Kamil had visited Wash U and I had visited U Minn. A provisional partnership was established that was firmed up by mid-September. In the ensuing two months, a fast-and-furious effort carried us to the finish line. It included quickly pulling together preliminary data on many fronts (benefiting from the earlier efforts of Alex, Matt, and Tim with the Pittsburgh Brain Competition), coupled with intense discussions on how we would propose to acquire and analyze data from four MRI modalities plus MEG. Discussions were intense and sometimes chaotic, but the sense of enthusiasm and excitement allowed the multi-institutional consortium to focus and pull together when the chips were down. On a different front, we were also successful in obtaining major institutional commitments

(totaling $4 million, or more than 10% of the amount to be awarded) from the dean of the Medical School, the Department of Radiology, and the McDonnell Center for Systems Neuroscience, which greatly strengthened our cause. The 90-page research proposal (360 pages all told) was submitted just before Thanksgiving in 2009. Just before the deadline, I discovered that the supposedly final text was a full two pages over the limit; I worked late into a Saturday night wordsmithing the document until it was under the limit! Altogether the proposal represented a monumental effort by many staff and investigators at many institutions. While they are too numerous to mention individually, I consider it especially important to commend Lucille Miller (who handled the budget) and Susan Danker (my administrative assistant), as key staff are too often unsung heroes in projects like this.

Then the wait began. In early March of 2010, we received reviews of our proposal and learned that we were in the running, but that a different proposal was in the lead. We wrote a detailed response to the criticisms and concerns expressed by the reviewers, then waited further. As it happened, several of the contenders were at a meeting on "Connectomics" organized by Sebastian Seung and held in Seoul, Korea, in late March, as the decision time was nearing. It made for a few awkward conversational moments. While en route back from this meeting, I landed in Dallas and read an e-mail from Mike Huerta asking me to give him a call. I had a close connection, so had to wait on pins and needles until I arrived in St. Louis to learn that our consortium would indeed receive the full award. (In addition, NIH made a separate grant to the MGH/UCLA consortium to enable them to build and use a customized scanner, highly specialized for diffusion imaging.)

There was great excitement over receiving the main HCP award. Isabel and I hosted a memorable party at our house to celebrate the good news. Then we quickly shifted our attention to the serious business of getting plans into motion so that the project would get off to a fast and good start. One of the first orders of business was to identify a project manager having the skill sets to help oversee and coordinate a bunch of academics, most of whom had never been involved in a project of this scope or technical demands. We recruited Sandy Curtiss, a PhD molecular biologist by training who had worked in industry for many years but who also had experience in academia and appreciated the cultural differences. I found it tremendously enjoyable working with Sandy; we have had lots of laughs plus a few tears as we jointly worked through an immense variety of issues large and small in order to keep the project on track. Susan Danker aided tremendously on the administrative side, as did Lucille Miller, Tami Evans, and several others in our departmental business office. We recruited Jennifer (Jenn) Elam as an outreach coordinator, and she has done yeoman's work in building a very successful outreach effort.

On the scientific and technical fronts, well over 100 investigators, students, and staff have been heavily involved in the HCP effort over the past five years. We held an intensive two-day All-Hands Meetings at Wash U each fall and another equally intensive two-day Many-Hands Meeting at U Minn each spring. These were very useful for building up camaraderie and team spirit at the outset and sustaining momentum in the later years as we worked through a wide range of technical challenges. We collectively came to appreciate the complementary expertise of the different consortium sites. The Minnesota team (Kamil, Essa Yacoub, and many others) is especially strong on issues relating to MRI scanner hardware, pulse sequences, and initial stages of data processing. The group at the Oxford Centre for Functional MRI of the Brain, led by Steve Smith, Tim Behrens, and Mark Jenkinson, is especially strong in the area of data analysis for fMRI and diffusion imaging. Our other European colleagues provided key expertise in the analysis of MEG data. Finally, the Wash U group, including Deanna Barch, Mike Harms, Greg Burgess, and many others, provides expertise in neurobiological issues and task fMRI methods. Cindy Hernke capably led a team of research assistants who coaxed 1,200 subjects to be remarkably cooperative as they each lay very still in the scanner for four 1-hour scan sessions. Erin Reid has been the walking definition of how to carry out systematic quality control of structural imaging data on every one of these subjects.

Having invested two decades in various aspects of neuroinformatics, broadly writ, it has been especially rewarding to see neuroinformatics play a key role in the HCP success. This includes two broad aspects. Dan Marcus (my former graduate student turned neuroinformatician par excellence) spearheaded a large neuroinformatics group with whom I worked very closely. They have implemented the ConnectomeDB database, which has proven to be a user-friendly workhorse platform for sharing the immense amounts of multimodal HCP data—nearly a petabyte (1,000 terabytes) by the end of the project. Complementing ConnectomeDB is the Connectome Workbench visualization and analysis software spearheaded by John Harwell, Tim Coalson, Matt Glasser, and others in my lab. Workbench is proving to be a worthy successor to our older Caret platform, having kept what is most useful and having added countless cool additional features for analyzing multimodal structural, functional, and connectivity data.

Major parts of the scientific and technical aspects of HCP data acquisition and early stages of data analysis (including the "minimal preprocessing pipelines") are described in a special issue of *Neuroimage* (Van Essen et al., 2013, plus seven other Wash U–Minn HCP articles cited therein). Many studies that make use of HCP data have been published (see http://www.humanconnectome.org), and there will be lots more in the coming years.

As I write this chapter, the Wash U–Minn HCP Consortium is wrapping up the five-year project, having successfully fulfilled its mission. As the main HCP winds down, NIH has decided to fund a number of other HCP-style

endeavors that are just starting to get under way. Three "HCP Lifespan" projects will enable examination of brain circuits in healthy humans during maturation and aging. Another set of projects is under the umbrella of "Connectomes Related to Human Disease." All of these projects will scan their participants using HCP-style advances in data acquisition, will process their data using HCP-style analysis pipelines, and will share their data on an expanded ConnectomeDB platform under the umbrella of the Connectome Coordination Facility that Dan Marcus and I will jointly lead. In short, there is life after the HCP, and it will be fascinating to see how the next stages of human connectomics unfold.

A few additional reflections on what has—and has not—been accomplished by the HCP seem in order.

The improvements in data acquisition and analysis achieved by the HCP include a few that represent major "quantum jumps." One is the use of multiband pulse sequences that greatly increase not only the amount of data acquired but also its overall quality. Another is the introduction of the CIFTI (Connectivity Informatics Technology Initiative) data format and the concept of "grayordinates" that include gray matter from both cerebral cortex (surface vertices) and subcortical nuclei (voxels) in a common data format. Numerous other refinements are more incremental in nature but altogether add up to large improvements in aggregate (Glasser et al., 2013a, in preparation).

Patience required. Earlier parts of the cartography story described the slow time course not only of achieving key methodological improvements, but also additional lengthy periods waiting for the field to capitalize fully on these advances. Cortical flatmaps—and their partners in crime, cortical surface models—have gradually but inexorably become mainstream, insofar as they are widely accepted as valuable modes of analysis and display. However, it remains a reality that the majority of neuroimaging studies that would benefit from using cortical surface models either fail to use them altogether or use them suboptimally. I learned a lot of patience in the first several decades of cortical cartography, and the need for sustained patience has not dissipated. Ways to accelerate progress in widespread acceptance of improved methods, not just in implementing the improvements, is an important issue for the future.

Cartography and parcellation redux. Accurate cortical parcellation, while something of a holy grail for more than a century, has indeed proven enormously challenging, but the HCP data have proven to be a gold mine for progress on this front. It is highly gratifying that a new multimodal human cortical parcellation has recently emerged, which identifies 180 cortical areas in each hemisphere (Glasser et al., in preparation). Particularly striking is the fact that a large majority (~90%) of cortical areas can now be robustly identified in a large

majority (also ~90%) of HCP subjects. This is a testament to the exceptionally high quality of the HCP multimodal data as well as the importance of continued methodological refinements. A host of interesting follow-up questions will loom as these data sets become freely available to the neuroscience community.

Be optimistic, yet critical of glasses half full and half empty. In talking and writing about connectomics over the past five years, I have split my "pitch" along two somewhat-disparate lines. On the one hand, there are excellent reasons to be enthusiastic and excited about the new methods and vast amounts of new, multimodal data to provide insights about brain structure, function, and connectivity, and their relationship to human behavior. On the other hand, there are major technical limitations to each modality, especially those relating to connectivity, that are seriously underappreciated in the neuroimaging and neuroscience community. Diffusion imaging and tractography have one set of major limitations; functional connectivity based on resting-state fMRI has another, very different set of limitations. We don't have "ground truth" in humans, but comparisons with data from nonhuman primates suggest that the glass is half full and half empty (e.g., Van Essen et al., 2014, Donahue et al., in preparation). This is not the place to delve into the technical details, but it is incumbent at all levels to strike a balance that doesn't oversell what can be done using current methodology.

Musings on the Mind

I close with a few more general remarks.

The advances over the past five decades in our understanding of the brain have been truly breathtaking. Yet I consider it equally fair to emphasize that neuroscience is still only scratching the surface in the effort to decipher many fundamental and profound mysteries of the mind.

In the realm of connectomics, the blogosphere is filled with chatter about how it may be possible "soon" (within decades) to map a complete human connectome across microscopic as well as macroscopic scales. Some respected scientists contribute to such speculation, but I consider it to be highly if not wildly optimistic. But I won't try to rule it out entirely, because I've taken pains in this chapter to emphasize how unpredictable our predictions to date have proven to be.

I do anticipate it will be possible to map a complete micro/macroconnectome of fruit fly (*Drosophila*), and even that of a mouse, where physical scale and tissue preservation issues are far less challenging. But this brings us to an even larger question that looms. Knowing a complete connectome, like knowing the exact architecture of a powerful computer, doesn't reveal exactly how or what information is processed and stored in that device in real time. And that's an extremely tall order, as I tried to touch upon in the sections on computational neuroscience and neural engineering.

Can the human brain ever "fully" understand the human brain? I won't say it's impossible, but frankly, I doubt it. If we ask whether chimpanzees could ever understand their own brain, the answer would be a resounding negative. Yet while we are obviously a lot smarter than other great apes, I think there are serious limits to human intelligence, even when aided by increasingly sophisticated and powerful computers. So what gives our species the chutzpah to think we have or ever might cross that divide? Pitted against our efforts to guess the pace of progress is what I consider the far more serious issue of dealing with the pace of regress, given our power to sow the seeds for devastating our planet and civilization. Let us hope that progress in neuroscience and in other fields will enable us to better modulate our base instincts and keep the species and our planet alive and well.

On a very different note, death of course comes to us all, in very different life stages and modes of occurrence. My family seems to have genes that enable longevity. My father passed away peacefully at the age of 92 after a long and full life and aware that it had run its course. At the time of this writing, my mother is still going strong. My personal aspiration is not for longevity per se, but rather a fervent hope that fate delivers the opportunity to enjoy and remember life with family and friends until it is over.

Finally, I express my immense thanks to all who have helped directly and indirectly to contribute to a truly exciting and rewarding scientific joyride over many decades. Special thanks to Isabel, who has been extremely supportive and tolerant for lo these 46 years. To restate what we had imprinted on a T-shirt made for our 40th anniversary, "What a trip!"

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