Frederick A. Miles

Born:
Grimsby, England
December 4, 1939

Education:
University of Leeds, BSc (1962)
University of Sussex, PhD (1971)

Appointments:
Schoolmaster, Foxwood School, Leeds, England (1962–1966)
Assistant Lecturer/Lecturer, University of Sussex, England (1966–1971)
Visiting Fellow/Associate/Scientist, Laboratory of Neurophysiology, National Institute of Mental Health, National Institutes of Health (NIH) (1971–1980)
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Golden Brain Award of the Minerva Foundation, Berkeley, CA (2000)
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Frederick A. Miles did his earliest research on the centrifugal innervation of the avian retina and described its effects on the receptive field properties of the retinal ganglion cells. All of his subsequent work has been on primate eye movements. In an early project, he designed optical devices to alter the gain of the rotational vestibulo-ocular reflex and obtained neurophysiological evidence that the underlying changes were occurring in brain-stem pathways. After using a variety of optical techniques to demonstrate other forms of adaptive plasticity, his laboratory went on to discover three independent visually driven ocular reflexes that responded with ultra-short latency: one tracked linear motion and was postulated to work in concert with the translational vestibulo-ocular reflex with which it shared a dependence on the inverse of the viewing distance; the other two reflexes generated vergence eye movements, one in response to binocular disparity and the other in response to radial optic flow. All of these reflexes had special features that would help them to function effectively in a complex 3-D visual world and were critically dependent on the Fourier composition of the stimuli, consistent with early spatiotemporal filtering as in energy models of motion and disparity detection. Later work, using broad-band stimuli, uncovered nonlinearities that were attributed to mutual inhibition between the mechanisms sensing the motion or disparity of the different harmonic components. Two significant outcomes, considered vital for optimal performance: local winner-take-all behavior favoring the most salient harmonic, and global divisive normalization reducing dependence on image size. The local spatiotemporal characteristics of the reflexes of humans strongly resemble those of neurons in the monkey's striate cortex, suggesting that they provide insights into the processing of visual motion and binocular disparity by the human striate cortex.

Frederick A. Miles

The Early Years

I was born in Grimsby, a fishing port on the east coast of Lincolnshire (England), just after Britain entered World War II. The war and its aftermath were to dominate my early life. We lived in a row house in a working class area of town, and my father was called up for military service in June 1940, when I was six months old. He was small and could drive a car, qualifications that got him into the Royal Armoured Corps as a tank driver. He was taken prisoner in North Africa by Rommel's Afrika Korps outside Tobruk in early April 1941. After a period in a prisoner of war (POW) camp in Italy, he was transferred to a camp in Upper Silesia. In January 1945, as the Russians were rapidly approaching from the East, his camp—along with many others in the area—was quickly evacuated. The prisoners were force marched westward toward Czechoslovakia. It was a particularly severe winter, and there was no food except what could be scavenged from the mostly deserted towns and villages. Stragglers were shot. One morning, however, the prisoners awoke to find that the guards had left. After a period of indecision, the prisoners split up into small groups and my father's group (of seven) set out to reach Prague. After various tense encounters, including one with a band of heavily armed Russian women, my father's group eventually made it to the U.S. Embassy in Prague. Almost immediately, he found himself seated on the floor of a U.S. Army Air Force transport plane flying to Lydd in southern England.

On arriving in England some time in 1945, my father learned that our house in Grimsby had been bombed and that I had been taken in by a couple who lived in the next street. Apparently, on the night of the bombing, I had taken refuge in their outdoor toilet. I have since learned that the bombing started at 1:43 a.m. on June 14, 1943, lasted about an hour, and was the worst of the 37 bombing raids on the town during the war (Smith, 1983). My memories of that night are scant. I recall being in an air-raid shelter in a neighbor's backyard when suddenly the houses seemed to be engulfed in flames. Soon after, everyone left the shelter. I vaguely remember wandering the local streets but do not recall taking refuge. I did not know that, in addition to the usual incendiary and high explosive bombs, more than 3,000 anti-personnel cluster bombs—commonly called "butterfly bombs"—were dropped on the town that night (Smith, 1983). These butterfly bombs, which were designed to arm only *after* they had landed and then to explode when disturbed, accounted for many of the 66 deaths in the town that night, but

I was unscathed. I do not know where my mother was during the bombing, but it was not unusual for her to leave me on my own, even overnight. I had two sisters—one older and the other younger—who were living with my father's parents in another part of the town. I do not know why I was not with my sisters.

The couple who had taken me in, Maurice and Olive Pimperton, were in their late forties. An incendiary bomb had gone through their roof, landing on their bed without detonating, and Mr. Pimperton had carried it to the river at the end of the street and thrown it in. The Pimpertons had both left school at the age of 12 to make a living and had a married daughter who lived with them; her husband was in the army and would take part in the Allied invasion of Italy later that year. Mister Pimperton (later, I would call him, "Dad Pim") worked as a locomotive engineer ("train driver") for the London and North Eastern Railway, while his wife took care of the home, and their daughter served behind the counter in a local grocery shop. After the bombing, my mother had relocated to a house about half a mile away in a somewhat poorer area near the docks and, after a time, I joined her. The house abutted a sawmill and was infested with rats and cockroaches. My mother's absences grew more frequent, and I would befriend other children partly in hopes of being invited in for a meal. However, this situation did not last long. It so happened that the Pimperton's daughter was one of our local air raid wardens, and while on duty one day she saw me on the street. She insisted that I go home with her—apparently, it was clear that I was not being cared for—and I never returned to live with my mother. The Pimpertons raised me as their son, and I became deeply fond of them. I am not aware that my mother made any attempt to take me back, and I long thought that she had completely disappeared from my life. However, she was to make a dramatic, if brief, comeback some years later when I was in college.

The first time that I remember seeing my father was when he stepped off the train at Grimsby Town Railway Station on his return from the war. I do not remember much other than thinking that he was the thinnest person I had ever seen. After his return, my father lived with his parents, along with my two sisters, while I continued to live with the Pimpertons. Not long afterward, my father came to see me at the Pimperton's home. It was late evening, and I was in bed. Dad Pim woke me and told me that my father wanted to ask me a question—he wanted to know if I would like to go and live with him. Without hesitation, I indicated that I wanted to stay with the Pims. I provided no explanation and none was sought. My father accepted my decision without protest and made no attempt to enlist my sympathy for his predicament, which was even worse than I knew. I was aware that he had been a POW for some years, but I did not know that some time after I moved in with the Pimpertons, my mother had had an illegitimate son who was raised by her sister. (I did not learn that I had a half-brother until

I was in college, and I have not seen him for half a century.) My parents soon divorced, and my father married a widow; her husband had been a fisherman who had died when his trawler struck a mine. My father and his new wife later had two daughters, and I would see them occasionally; but I lost contact when I was in my late teens. It was almost half a century before I saw him again, after locating his whereabouts on the Web in 2002; only then did I learn the full extent of his harrowing wartime ordeals.

The Pimpertons always treated me as one of their own. In fact, I was aware that Mam Pim (as I called Mrs. Pimperton) doted on me. Overt displays of affection were not the custom, but I was never in doubt that I was a cherished member of the family. The Pimpertons' house was small and there were few luxuries; they never had a refrigerator, a car, or a telephone, for example. But they were frugal and resourceful—growing their own vegetables and raising pigs, chickens, and ducks on a nearby allotment—so we always ate well even during the worst of the rationing. Unbeknownst to me, the Pimpertons had wanted to make their adoption of me official, but my father would not agree to it and, much to their disappointment, had insisted that I keep his name, "Miles." (The irony of this is that my father was to discover much later that "Miles" was not his real name. He too had been adopted, though it was never made official, and only in 1983 did he discover that the name on his birth certificate was actually "Foxon." Before visiting us in the United States in 2003, when he was age 89, he insisted on changing his name to "Miles" so that his passport would be in the name by which he had been known all of his life.)

When I was five years old, I entered the local primary school (Macaulay Street), which I really enjoyed. I had decided that I wanted to be a doctor but, of course, nobody took me seriously; at that time, I did not even know anyone who had been to a university. There were almost 150 children in my year at school, which was divided into three classes. In 1950, when I was 10 years old, I was one of four children that year who passed the so-called eleven-plus examination and went on to Wintringham Grammar School. The 1944 Education Act had made provision for working-class children like me who "passed the scholarship" to attend grammar schools free of tuition. These schools prepared children for examinations that could eventually allow them to qualify for admission to a university.

Wintringham was the only grammar school in Grimsby, and it was on the other side of town. Neither I nor my friend, Tony Wass, who had also passed the eleven-plus, knew its exact location. Our solution was to cycle into town, find another boy wearing the same uniform, and follow him to the school. From the very beginning, the Pimpertons had always given me complete freedom to come and go as I pleased, and they seemed to assume that I could deal with any eventuality. They knew little of what I was doing at the grammar school but were always very supportive. Many of the pupils there were from middle-class homes, and I generally kept my personal

history to myself, in part because it was not usual to talk about wartime experiences and in part because I was ashamed of being adopted. I acquired a lifelong interest in classical music when I was a teenager, thanks largely to an older school friend, David Cressey, who had a record player. We were both besotted with the then-recent recordings of Bach's "48 Preludes and Fugues" by Rosalyn Tureck and Beethoven's late quartets by the Budapest String Quartet. David went on to read Greats at Oxford, but I was not a very good student. With a few notable exceptions, I found the teaching at Wintringham uninspired and somehow there were always too many other distractions. Also, I have always preferred to learn from the written—rather than the spoken—word and generally found an hour in the library more informative than an hour in the classroom or lecture hall. Unfortunately for me, good books—especially in science—were in very short supply at the grammar school, and the public library was even worse. (It did not help that both had suffered major bomb damage.) Nonetheless, I managed to gain entry to Leeds University Medical School in 1958. I was 18 years old and simply not mature enough to meet such a challenge.

Medical School

In England at that time, 4.4 percent of the age group went on to a university (Layard, King, and Moser, 1969), and tuition was free. Students like me from working-class homes received grants to cover their accommodation, meals, travel, books, and so forth. One had to be very frugal to make ends meet, but I was used to austerity. Dad Pim was nearing retirement age, and his job did not provide a pension so the Pimpertons were not in a position to help me financially. It was the first time that I had lived away from home and in a large city. The atmospheric pollution was severe, resulting in almost perpetual twilight in winter; visibility could be reduced to a few yards, and all of the older stone buildings downtown, such as the town hall, were completely black from the pollutants. There were also still slums in Leeds at that time, and it had the feel of a hardscrabble northern city. I had been very disappointed with my academic performance in grammar school and was determined to do better at medical school. In my first year, I lived in a series of boardinghouses that had no study facilities, and I relied on the work spaces in the university (Brotherton) library, which was often crowded. Fortunately, the academic load in my first year was very light; and by the start of the second year, when the work load was very heavy, I had my own room and a small desk. The heating in my room was often inadequate but a blanket wrapped around the shoulders helped a lot in winter. Lectures, laboratory classes, and tutorials took up every weekday, as well as Saturdays until 1 p.m. Keeping up with assignments meant working late most evenings and through the weekend, especially because I found many lectures inscrutable and relied heavily on textbooks to learn the material.

At first, I was strongly motivated, but gradually I became disenchanted, especially with the emphasis on rote learning, and soon reached the conclusion that I had made a mistake in choosing to study medicine. Without consulting anyone, I secretly decided to quit. But how could I earn a living? I was 20 years old with neither money nor marketable job skills. Transferring to another school at the university was not an option—the system was not flexible enough for that. I did not want to leave the university without a degree, but the prospect of continuing to study medicine for several more years was unthinkable. My salvation came in the form of a bachelor of sciences (BSc) course in physiology, which was offered to a small number of medical students after they had completed pre-clinical medicine ("second MB") and, importantly for me, it required only one year of study. The purpose of this course was to provide medical students with a more advanced experience of laboratory science and was not meant to be an end in itself. I applied for the course and, in 1961, after completing second MB, I was accepted.

However, a few months before second MB finals, I had learned from my older sister (who had managed to stay in contact despite everything) that our mother, whom I had not seen or heard of for more than a decade, was in a hospital in Grimsby and wanted to see me. My sister explained that our mother was an alcoholic and had collapsed drunk on the street late one winter evening, suffering severe frostbite that had resulted in the amputation of one hand and one foot. With some trepidation, I went to see her in the hospital. I was shocked to see her; she was emaciated, her hair was thin and unkempt, and she was missing some teeth. What remained of her foot was protected from the weight of the bed covers by a cage and the remains of her hand were heavily bandaged. Despite appearances, she was extremely cheerful—even euphoric—and, to my embarrassment, very eager to show off her son to the other patients and nurses. She behaved as though we had a close and loving relationship. Somehow she knew that I was a medical student at Leeds and told me that some years previously she had lived for a time in that city, which was about 75 miles from her hometown of Grimsby. I was amazed to learn that she had served behind the bar in the pub frequented by the medical students! Stranger still, she had lived for a time with an artist there who "painted pictures of dead people at the medical school." That was the last time I saw my mother. We made no plans to meet again, and she died a few years later. I have no photographs or mementoes of her. Almost certainly, the artist whom she had mentioned was a painter who occasionally lectured the medical students on art. I had recently heard one of his lectures and seen his paintings, including one of a cadaver, in a large retrospective of his work at the Leeds City Art Gallery, which was just a few blocks from the medical school. I recently learned from an assistant curator that the Leeds Art Gallery—as it is now known—has a painting of a cadaver entitled, "Clay," by a well-known local artist, Jacob Kramer (1892–1962), who had a retrospective at the gallery in 1960. According to his

biographer, Kramer lived near the medical school, had friends on the faculty, and frequented the medical students' pub (Manson, 2006).

I mostly enjoyed the physiology course, especially the opportunity to sit in on faculty research projects. Intellectually though, the highlight was undoubtedly reading the papers of Hodgkin and Huxley: for the first time I realized that science could be wonderfully elegant as well as rigorous and complex. This was a revelation to me—a quantum step in my appreciation of what science could be—and Hodgkin and Huxley's voltage clamp papers are surely among the supreme achievements in neuroscience.

School Teaching

After obtaining a BSc in animal physiology, I left the medical school with the unrealistic notion that I could earn a living by writing fiction. It was 1962, and a year earlier I had met, and soon married, Jennifer, who was a nurse and the only girlfriend I ever had. At first, we lived on her modest income, but when Jennifer became pregnant, it was evident that I would have to earn a living and put aside "the great novel." At a friend's urging, I took a position teaching science at Foxwood School, one of the first purpose-built comprehensive schools in Great Britain, located on a large housing estate in northeast Leeds. At that time, a degree was sufficient qualification to teach in a secondary school. This was a boys' school, with ages ranging from 11 to 18 years, and catered to all abilities (except boys with very special needs). I found teaching there hugely stimulating but also extremely demanding, requiring long hours preparing classes, setting up the laboratory equipment, and grading papers, in addition to the rather full teaching schedule. Like most of the teachers at the school, I had strong leftist sympathies and was drawn to its egalitarian approach to education, which was in stark contrast to my own elitist grammar school background, and I felt that it was a very successful educational experiment. However, I gradually became overwhelmed by the heavy teaching load and found myself unable to compromise in an acceptable way. Jennifer suggested that I would fare better teaching in a university, an idea I dismissed as completely unrealistic, given that I did not have either a doctorate or publications.

The University of Sussex

But Jennifer persisted and, when I was in my fourth year of teaching at Foxwood, she saw an advertisement in *The Times Educational Supplement* for a tenure-track faculty position at the University of Sussex, one of several new universities that had opened in Great Britain in the 1960s. The School of Biological Sciences was looking for someone to develop laboratory materials that could be used in the teaching of modern biology in secondary schools—a very unusual position. Jennifer argued that I had the requisite

experience, but I was unconvinced and thought it would be a complete waste of time to apply. In those days, one filled in application forms to apply for such a position and, undaunted, Jennifer sent off for the forms. She then cajoled me into filling them in and mailed them. To my surprise, and embarrassment, I was called for interview.

During the interview, I was seated at one end of a long table with faculty members seated on either side and John Maynard Smith (JMS), the dean of the school, at the far end. JMS presided over the interview and started by telling me that the position for which I had applied had already been given to someone else. However, he asked me if I would like to be considered for another position—a tutorial fellowship—that was funded for three years, was not tenure-track, and involved teaching mammalian physiology to the undergraduates. It sounded interesting and I saw little to be lost in allowing myself to be considered—though I was convinced that I had no chance of getting it. JMS asked all the questions and was merciless: Why did you quit medicine? You took a first in physiology, yet you quit that too—why? Why did you choose to teach in a comprehensive school? Why are you now proposing to give up this teaching job? My answers were weak but truthful, along the lines that I had not realized that medicine was not a science, that the physiology degree was undertaken mostly to get an academic qualification, that I liked the egalitarian approach of the comprehensive schools but that I was overwhelmed by the workload. JMS went on to indicate that all faculty at Sussex were expected to do independent research and asked about my research plans. When I indicated that I did not have any, JMS persisted by pointing out that my physiological studies centered mainly on neurophysiology and cardiovascular physiology and, if I were to do research in one of those two areas, which would it be? I indicated that I thought neurophysiology was the more interesting and with that the interview ended abruptly.

I was convinced that the interview had been an unmitigated disaster and returned to Leeds assuming that that was the last I would ever see or hear of the University of Sussex. However, there were a number of things that I did not know about the university and JMS that perhaps worked in my favor. The School of Biological Sciences had opened only a year earlier and had been unable to recruit anyone to teach mammalian physiology—perhaps because there was neither a medical school nor a department of physiology at Sussex. I knew JMS only as a world-renowned theoretician in evolutionary biology and learned only later that he was not enamored of medical schools as centers of learning or research, had started out as an engineer and only later switched to biology, did not have a doctorate, and was politically on the far left. Perhaps this predisposed JMS to be sympathetic to a failed medic with leftist sympathies and unrealistic career goals? In any event, to my surprise and delight, I was offered a position and assigned to the animal behavior group headed by Richard Andrew. Even more remarkable, when I arrived in Sussex, I found that by some clerical error I had been

given an assistant lectureship, which was a tenure-track position. I was well aware that others in the school with assistant lectureships had doctorates, publications, and were conducting independent research. When I spoke with JMS about it he denied that there had been any clerical error, and I kept the assistant lectureship. Such things would be unthinkable nowadays. (Even at that time it was extraordinary.) With such great fortune, I surely had a charmed life. I saw this as my chance to make up for all my previous failures and vowed to do everything I could to justify Sussex's confidence in me. By that time, Jennifer and I had two sons, Richard (born 1962) and Graeme (born 1964), and the move from the northern city of Leeds to the southern rural village of Ringmer in Sussex—10 miles from the university—was a huge change for all of us.

It was 1966. The School of Biological Sciences had opened only the year before so most of the teaching curriculum had still to be decided, and the student teaching laboratories had to be equipped and made operational. I had been assigned an office/laboratory and, because I was the first occupant, I had access to some (rather limited) funds to equip it. But before I could do that I had to come up with a research project. Thomas Collett, who—apart from Richard Andrew—was the only other member of the animal behavior group at that time, was doing single unit recordings in the moth's visual system and suggested that I might get some ideas from the recent papers of two scientists working in the United States: Hubel and Wiesel. I had never heard of them, and I found their papers exhilarating. After only a few hours in the library, I had decided that I would do single unit recordings in the visual system! I did not have any research experience, and my laboratory was an empty room. Also, I did not have the funding (and the school did not have the facilities) to support research on cats, the preferred animal for visual studies at that time. At this point, Richard Andrew suggested that I work on birds—he was studying self-stimulation in domestic chicks, which he collected each week from the hatchery, and always had a few surplus that he would be happy to make available to me. The problem with this was that I had worked only on mammals—mostly humans and cats—and knew absolutely nothing about the anatomy or physiology of birds. But after a few more hours in the library, I came up with a general plan to adapt the methodology previously used on cats by Hubel and Wiesel (and others) to newly hatched chicks. However, I still did not have a specific project. Once again the library came to my rescue. A recent issue of the *Journal of Anatomy* contained two papers that described an anatomical projection from a nucleus in the mid-brain of the pigeon, called the isthmo-optic nucleus (ION), to the contralateral retina (McGill, Powell, and Cowan, 1966a, b). This study reported that the ION received a visual projection from the contralateral eye via the tectum that was retinotopically organized and in turn projected back to that same eye, as though part of a closed-loop feedback system. These were anatomical studies, and

nothing was known of either the physiology or the function of this centrifugal projection from the ION to the contralateral eye. I thought it would be interesting to characterize the visual receptive field characteristics of the retinal ganglion cells (RGCs) and to find out how they were affected by electrical activation of the centrifugal fibers. I was also interested in the visual receptive field properties of the centrifugal neurons and the effect of lesioning these neurons on the chick's visual behavior.

There had been few neurophysiological studies on birds at that time so there was no established methodology, and I had never worked on the visual system of any animal. Basic things such as anesthesia of newly hatched chicks had already been worked out by Richard Andrew, but many pilot studies were needed to work out how to prepare the birds for single unit recording. There were many methodological questions: How to apply controlled visual stimuli to characterize visual receptive field properties? How to immobilize the eye while characterizing the visual receptive fields? How to refract the eye so that images were focused on the retina? How to ventilate the paralyzed animal given that they have lungs and air sacs? How to maintain the animal's body temperature? (The oldest birds I worked on were less than two weeks old and were not able to thermoregulate.) How to monitor the chick's physiological condition during recording? How to locate the ION, whose dimensions were approximately $0.8 \times 0.3 \times 0.3$ mm, especially given that the skull was largely cartilaginous and hence difficult to position accurately in a stereotaxic device (even supposing I had one)? The funds available to equip my office were sufficient to purchase some basic equipment such as an oscilloscope, a Grass stimulator, a pair of Narashige micromanipulators, a Tektronix pre-amplifier for unit recording, and an FM tape recorder for archiving data to allow later quantitative analysis. Fortunately, Thomas Collett was using micropipettes to record unit activity and was happy to allow me to use his equipment to pull microelectrodes. Everything else I would have to construct for myself.

Fortunately, the school had a machine shop and two machinists, who instructed me in the use of the milling machine, lathe, and so forth, and permitted me to fabricate my own equipment. I put together a stable recording platform, a stereotaxic device to hold the chick's head in place and support the Narashige micromanipulators needed to position the recording micropipettes as well as stimulating electrodes and (later) cooling probes. I also constructed two slide projectors, each equipped with two electromechanical devices—one to operate a shutter to permit precise timing of stimulus onset/offset and the other to move the projected slide at a specified velocity (under feedback control) to apply controlled motion stimuli—and Dove prisms to rotate the images. A back-projection screen with half-silvered mirrors in the two projection paths (to deflect the images onto a plotting table to facilitate the mapping of the visual receptive fields) completed the visual stimulation equipment. I also built a motor-driven microsyringe to provide an

intravenous drip of muscle relaxant (at a controlled rate of one-tenth of a milliliter per hour) to immobilize the eyes. Ventilation of the paralyzed bird was provided by flushing air with 5 percent carbon dioxide through the lungs and out through a tube introduced into the abdominal air sac, a technique that had been pioneered on adult chickens by Fedde, Burger, and Kitchell (1963). I also decided to canulate the main artery in the leg and monitor the blood pressure with a half-bridge variable reluctance transducer to monitor the bird's physiological condition. The chick's small size meant that all surgery had to be done under a dissecting microscope. Whenever I encountered a problem, there was always the library.

Given that I also had a full teaching load of lectures, tutorials, grading essays, and so forth and was heavily involved in developing the new curriculum and putting together the new teaching laboratories—there were no teaching assistants—it was perhaps not surprising that it took almost two years before I was ready to begin single unit recordings. Toward the end of my first year, I benefitted from yet another clerical error: I received a letter informing me that I had been promoted to a full lectureship, which was a tenured position, even though I had yet to record any data and had no publications. Once more, JMS denied that there had been any error and so I was in the embarrassing position of having a tenured faculty position while many others, who were much better qualified, did not. I still find it hard to understand how this could have happened. It meant that I now had complete freedom to do whatever I wanted with minimal outside interference; and over the next two years, I did a series of experiments on the chick's visual system.

My first study characterized the visual receptive field properties of the RGCs and indicated that many had on/off excitatory centers and purely inhibitory surrounds. Other RGCs were especially sensitive to motion and showed strong directional selectivity. These experiments were relatively straightforward and served to get me started.

My second study characterized the visual receptive field properties of the centrifugal neurons in the ION, which were identified by antidromic activation of the isthmo-optic tract (IOT) carrying their axons to the contralateral eye. Pilot experiments had established the stereotaxic coordinates of the ION, using electrical stimulation of the optic nerve head in the eye to backfire the neurons in the contralateral ION and using the collision test to establish that the recorded neurons were indeed transmitting impulses toward the eye. However, stereotaxic coordinates alone were not sufficient to identify ION neurons with certainty, and placing the stimulating electrodes on the optic nerve head to backfire the centrifugal neurons compromised vision, ruling out the possibility of examining the visual receptive field properties of the ION neurons. The anatomy indicated that the axons of the centrifugal neurons crossed over to the contralateral side and passed just under the roof of the midbrain. I had found that removing the forebrain

allowed excellent visualization of the roof of the midbrain and, remarkably, there was a white band clearly visible with the dissecting microscope, which when electrically activated reliably backfired neurons in the ION that had been previously identified by stimulating the optic nerve head in the contralateral eye. This was a critical methodological breakthrough and meant that I could now leave the contralateral eye intact. After opening the feedback loop (by sectioning the IOT) and identifying individual neurons in the ION (by electrically activating the IOT proximal to the cut), I could now present visual images to the contralateral eye and characterize the receptive field properties of the centrifugal neurons in the ION. This indicated that the receptive fields of the centrifugal neurons were more than an order of magnitude larger than those of the RGCs and were retinotopically organized (in accordance with the anatomical descriptions). The centrifugal neurons were also very sensitive to motion with a strong preference for forward movements through the visual field, dark vertical edges being particularly effective.

In a third study, I opened the feedback loop, again by sectioning the IOT, and recorded the effect of electrical stimulation of the IOT distal to the cut on the activity of the RGCs recorded in the contralateral eye. Activation of the IOT alone did not bring out activity in the generally silent RGCs. Occasionally, activation of the IOT increased the RGC responses to a spot flashed at the field center (as though facilitating the excitatory mechanism) but more commonly this too was without effect. Also, flashing an annulus in the "purely inhibitory surround" of the RGCs was without visible effect with or without stimulation of the IOT. However, when the excitatory field center of the RGC was activated with a spot while the inhibitory surround was activated simultaneously with an annulus so that there was no net excitation, stimulation of the IOT now brought out clear activity in the RGC. I reasoned that the centrifugal input must be suppressing the surround inhibition and thereby uncovering the central excitation, an example of activation by *disinhibition*.

My fourth study left the feedback loop intact and attempted to demonstrate centrifugal disinhibition using visual—rather than electrical—activation of the ION neurons. The plan was to first map the receptive field of a RGC and then stimulate it with a large centered spot that encroached on the surround to a sufficient extent that the central excitation was balanced by peripheral inhibition (i.e., there was no net activation). I expected that in such a situation the RGC would be very sensitive to any centrifugal disinhibition, and I proposed to then activate the centrifugal neurons by moving a large vertical dark edge forward through the visual field. I postulated that the dark edge would leave a trail of centrifugal disinhibition in the RGCs in its wake that could then be detected by applying the large-spot stimuli. (Fortunately, most RGCs were minimally responsive to the moving edge alone.) The edge occasionally brought out RGC responses to the large spot but, unfortunately,

it was entirely possible that this was due to interactions within the retina and not the result of disinhibition by the centrifugal input. In order to show that the responses to the large spots were due to centrifugal disinhibition, I blocked transmission in the IOT with a cooling probe. To be sure that the cooling probe was effective, I placed stimulating electrodes on the IOT distal to the cooling probe and a recording micropipette in the ION (in addition to the micropipette in the retina), allowing me to show that neurons in the ION could not be backfired from the IOT when the probe was on. I did many experiments but only in four cases did the edge bring out RGC responses to the large spot that could be eliminated by cooling the IOT. The low success rate was unfortunate, but the experimental design was too complicated and too many bits of apparatus had to work to get a positive result.

My fifth and final study on the ION was a collaboration with a graduate student in Richard Andrew's laboratory, Lesley Rogers. I reasoned that the centrifugal disinhibition of RGCs would have the effect of *increasing the excitability* of the RGCs and *reducing their spatial selectivity*, thereby increasing the bird's ability to *detect* images (but perhaps degrading its ability to discriminate their physical form). The finding that the centrifugal neurons were activated by vertical dark edges moving forward through the visual field led me to wonder if this meant that the centrifugal neurons were activated by local patches of shadow such as those encountered by the chick while feeding in undergrowth. Perhaps regions of the retina thrown into shadow by the chick's searching gestures while ground feeding would be subject to centrifugal disinhibition, rendering those regions more sensitive and less selective, and thereby increasing the chance that the chick might detect items of interest in the shadowed areas. Lesley Rogers had been studying the chick's pecking behavior, including its ability to discriminate food grains from pebbles, and I asked her to look at the performance of chicks with electrolytic lesions of the ION. The study included sham-operated controls, and Lesley did not know which chicks were controls and which had been lesioned. Lesley found that, when the floor was illuminated with a projected checkerboard pattern of light and dark squares, lesioned birds were almost as good as controls in the light squares but performed close to chance levels in the dark squares, consistent with the idea that the centrifugal system assisted the bird's visual search in shadowed areas. Lesley made a number of other observations on the lesioned birds, but this was the one most relevant to my recordings.

As I began to prepare these data for publication I began to also think about visiting the United States where a lot of exciting neuroscience was being done. At that point (1970), I had visited only one other laboratory—the department of anatomy at Oxford, where all the recent anatomical work on the ION had been carried out—and I had never attended a scientific meeting. Essentially, I was working in complete isolation and relied entirely on the literature for my information—though Richard Andrew and Thomas

Collett were always very helpful and remarkably knowledgeable. Richard suggested that I take a year's leave of absence to visit the United States and this was very appealing to me. Of course, I would have to find my own funding, and the university would have to hire someone to do my teaching. I started to think of new projects and of labs in the United States where I might be able to do them—the idea being to broaden my research experience and bring me into contact with other neuroscientists.

One of the undergraduate courses that Thomas and I had developed together had applied control theory to neural systems, and this had led me to explore the literature on the neural control of eye movements, a field that had applied this approach with considerable success using what was at that time a novel new method: single unit recordings in awake monkeys. This led me to formulate a project involving single unit recordings in the cerebellum of awake monkeys performing saccadic eye movements. I had the idea that the cerebellum might be part of a negative feedback control system that used short-latency inputs from extraocular muscle proprioceptors—recently discovered by Albert Fuchs and Hans Kornhuber—to compensate for variations in orbital viscosity. At that time, one of the pioneering laboratories engaged in single unit recordings in awake, trained monkeys was that of Ed Evarts at the National Institutes of Health (NIH) and I wrote to him, telling him about my research and asking if he could support me to work on this project in his laboratory for one year. At that point, my only publications were a monograph for undergraduates on conduction of the nerve impulse (Miles, 1969) and a short research paper in press in *Science* that described some effects of electrical stimulation of the IOT on RGCs (Miles, 1970). In any event, Ed wrote back saying that he could not take me because I did not have a doctorate. Richard Andrew immediately suggested that I register as a graduate student at Sussex (with him as my "official" mentor) and submit a thesis based on my chick work. (At that time, course work was not required for a doctorate.) I wrote back to Ed, telling him of my plan to obtain a doctorate, and he indicated that he still would not consider taking me until he had met and spoken directly with me. But Ed also said that this would not be a problem because he was coming to Europe later that year and would be happy to call in at Sussex to interview me. This was remarkably generous of him—he was already eminent whereas I was completely unknown—and he was as good as his word. I showed him my laboratory and my data, and he agreed to take me on as a visiting fellow provided I obtained a doctorate. In a very prescient aside, Richard Andrew opined that Ed probably ran a very tight ship.

And so it came about that I wrote a doctoral thesis, which I defended before two external examiners, Professor Patrick D. Wall from University College, London, and Dr. R. Michael Gaze from the National Institute for Medical Research at Mill Hill. The examination was held in Professor Wall's office at University College in August 1971 and, only a few days later, I left for the United States to work in Ed Evarts's laboratory at the NIH. The data

from the thesis were subsequently published in a back-to-back sequence of five papers (Miles, 1972a, b, c, d; Rogers and Miles, 1972).

The Move to the NIH

Academic stipends in England were not generous at that time, and it had been a constant struggle to make ends meet. The airline tickets for our journey to the United States represented a major expenditure. In order to keep within the 44-pound baggage allowance, we all wore our winter clothes (though it was August) and stuffed all of our pockets with the smaller items of clothing such as socks and underwear. At the flight check-in they insisted on weighing Richard and Graeme, who were deeply embarrassed at being asked to stand on the scale. We arrived in the United States with a total sum of $300, and within a few days it was almost all gone. Ed Evarts soon realized our predicament and kindly helped out by putting a deposit on an apartment for us. He also came up with some furniture from his basement, as did other scientists at the NIH, such as David Carpenter and Bob Wurtz. However, our predicament soon improved dramatically: Ed had arranged for me to receive a visiting fellowship from the National Institute of Mental Health (NIMH) ($7,000) and, in addition, a Fight for Sight Fellowship ($3,000) that, most importantly, was immediately paid in full. Suddenly, we were in Fat City.

The NIH turned out to be paradise for research—all the facilities one could hope for, no teaching, and no serious administrative responsibilities. Ed Evarts had inherited Wade Marshall's Laboratory of Neurophysiology in the NIMH a few years earlier and had facilities sufficient for several postdoctoral fellows to each have their own projects. When I arrived, Ed was recording in the motor cortex and Mahlon DeLong was recording in the basal ganglia. Many other postdoctoral fellows came to the lab while I was there including Hiroaki Niki, Jun Tanji, and Peter Strick. All were interested in the neural control of limb movements and used monkeys trained to manipulate a lever. I was interested in activity related to saccadic eye movements and trained monkeys on a visual fixation task using a protocol established by Albert Fuchs and David Robinson at Johns Hopkins and subsequently refined at the NIH by Bob Wurtz. Eye movements were recorded with Ag/AgCl electrodes implanted around the eyes. Everyone was very forthcoming with technical advice, and it was relatively easy to set up my lab. I also went to my first scientific meeting, which was also the very first meeting of the Society for Neuroscience, and there met many of the people who up to that point had been merely names on papers.

I had planned to spend one year in Ed's lab but, at his urging, I soon extended this to two years. Then, before I had completed my first year at the NIH and while still doing only exploratory recordings, Ed offered me a permanent position. At that time, one had to be a U.S. citizen to take a permanent position at the NIH, and in order to qualify for citizenship, one

had to have been a permanent resident in possession of a "green card" for at least five years. A further problem was that my J-1 visa required me to spend two years outside the United States before I could apply for a green card. Ed indicated that he would hold the position for however long it took for me to get U.S. citizenship. On this understanding, I resigned my position at Sussex. I did this with great regret; everyone there had been so kind and helpful, and it was the place where I learned my trade, so to speak.

Plasticity of the Vestibulo-Ocular Reflex

In the meantime, my experiments were not going well. I had great difficulty finding eye-movement-related activity in the vermal cerebellum and switched to recording in the medial vestibular nucleus in the brain stem, a known staging area for eye movements. This work resulted in one short conference paper of little interest, and I began to think of other more substantive projects. One of these concerned the long-term adaptive regulation of the gain of the vestibulo-ocular reflex (VOR). When I had first arrived in Ed's lab, all of the investigators were at a meeting of the International Union of Physiological Sciences in Munich, and when they returned all had been talking excitedly about Geoffrey Melville Jones's report that the human VOR could be altered by wearing left-right reversing prism spectacles. At that point, all I knew about the VOR was that it used information from the semicircular canals to help stabilize gaze during head turns by generating compensatory eye movements: when the head turned to the right the VOR rotated the eyes a roughly equal amount to the left. The VOR had been regarded as the very embodiment of a hard-wired reflex that operated open-loop—insofar as the semicircular canals that were ultimately responsible for eliciting the compensatory eye movements received no indication whether those eye movements were of an appropriate magnitude. Melville Jones's findings clearly suggested that this reflex was subject to long-term visually-mediated calibration.

A trip to the library revealed that Ito (1972) had recently suggested that the floccular lobes of the cerebellum were responsible for the adaptive control of VOR gain. The flocculus was seen as an inhibitory side-loop of the vestibulo-ocular pathway, receiving a mossy-fiber vestibular input and in turn projecting inhibition back onto the vestibular relay neurons in the brain stem via its Purkinje cell (P-cell) output. Brindley, Marr, and Albus had earlier hypothesized that the synapses between the mossy (parallel) fibers and the P-cells in the cerebellar cortex were modifiable and involved in motor learning, and invoked the so-called climbing-fiber input as the shaping influence. Ito was now suggesting that the climbing fibers might convey retinal image slip information to the P-cells in the flocculus to signal VOR gain errors and bring about appropriate changes in the efficacy of the vestibular parallel fiber inputs to the P-cells.

The clear idea here was that the VOR was subject to adaptive gain control, where gain is given by eye rotation/head rotation. One anomaly was that the reversing-prisms used to demonstrate this adaptive capability called for changes in *phase* rather than *gain*. Early in 1974, I decided to try the effects of telescopic spectacles, which I thought would present a more direct challenge to the gain of the VOR. I proposed to do this study on monkeys and decided to construct simple ×2 Galilean telescopes that would call for a doubling of the VOR gain; when reversed, they would call for a halving of the gain. I planned to construct the spectacles myself in the NIMH workshop, which I had already used for building other equipment. However, when I placed an order for the lenses, Ed Evarts—who had to approve all such purchases—called me into his office to ask why I needed the lenses. I told him that I was planning to construct a pair of telescopic spectacles for the monkey, but I did not get the opportunity to explain further: Ed became visibly angry and declared that it was "a stupid idea." I was stunned. I could see that Ed had made up his mind and was not prepared to discuss it. Although I had heard from others that Ed could be difficult, this came as a complete surprise. From that point on our relationship was never the same, though I was to remain in his lab for another six years. A major reason for my staying on after his angry outburst was that soon afterward he spent several months visiting various laboratories in the Soviet Union and left me in charge of the everyday running of his lab in Bethesda. After his departure, I immediately ordered the lenses, constructed the spectacles, and found that, over the course of a few days, monkeys wearing ×2 spectacles showed clear increases in VOR gain and monkeys wearing ×0.5 lenses showed clear decreases. I felt that this was the clearest evidence so far that the VOR was subject to adaptive gain control (often termed, adaptive plasticity). But now I had a problem: I required Ed's approval before I could submit a manuscript for publication. After agonizing over this for some time with another postdoctoral fellow, Jim Fuller, whom Ed had recently assigned to work with me, we decided to write a preliminary manuscript reporting these findings and simply place it on Ed's desk where he would surely see it when he returned. On his return, Ed made no immediate mention of the manuscript. One morning soon afterward, however, I entered my lab to find the manuscript on my desk with "approved" written across the title page and "delete" scrawled across a single paragraph inside. After the publication of that manuscript minus the offending paragraph (Miles and Fuller, 1974), telescopic spectacles became the standard technique for studying adaptive gain control of the VOR. Ed and I rarely conversed after that and, amazingly, he left me alone to do as I wished. Even more surprising, unbeknownst to me, Ed had persuaded the NIH to petition for a waiver of the J-1 foreign residence requirement; in 1975, I obtained a green card, giving me permanent resident status without having to spend two years abroad. At times, Ed could be very harsh and authoritarian, but at other times he could be kind

and generous. Several years later, Ed confided that he'd been "wrong about those experiments," but our relationship remained distant.

After Ed had allowed our paper to go forward, I plunged into studying the neurophysiological basis of the long-term adaptive control of VOR gain, with emphasis on determining the locus of the presumed underlying synaptic changes. The semicircular canal afferents were known to receive an efferent innervation from the brain stem and, given my previous experience with a centrifugal system, my initial thought was that these efferents might be mediating the gain adaptation. The recent classical recordings of Fernandez and Goldberg had shown that the canal afferents discharged as though encoding angular head velocity. Accordingly, I decided to examine the impact of changing VOR gain on the sensitivity of canal afferent fibers to sinusoidal angular oscillations of the whole animal about a vertical axis. This involved a statistical evaluation of populations of fibers recorded in the VIIIth nerve in normal and gain-changed monkeys—significant gain changes took many hours, so I did not think it feasible to record the impact of changing the gain on individual afferent fibers. It soon became evident that the VOR gain changes were probably not mediated by the efferents—though it would take quite some time to gather statistically convincing evidence.

Although this was very disappointing, the decision to start by recording in the VIIIth nerve turned out to be most fortuitous. I had recently visited Albert Fuchs's lab in Seattle and heard about some remarkable observations that he and his graduate student, Stephen Lisberger, had made while recording in the monkey's flocculus. They had found that the simple spike discharges of many P-cells (reflecting mossy-fiber inputs) modulated in phase with head velocity during angular oscillations about the vertical axis, as though driven by vestibular inputs from the semicircular canals, but *only* when the animal fixated a visual target that moved with the oscillating chair (i.e., when the monkey's eyes were roughly stationary in their orbits). Remarkably, there was little or no modulation when the oscillated animal fixated on a stationary target (Lisberger and Fuchs, 1974). Steve and Albert interpreted these findings as supporting Ito's idea that the flocculus was an inhibitory side-loop of the vestibulo-ocular pathway but offered no explanation as to why the P-cells' activity modulated *only* when the monkey fixated on a target that moved with the chair. Of course, this was especially interesting to me because of Ito's suggestion that the flocculus was the site of the modifiable synapses underlying the adaptive capability of the VOR.

As luck would have it, the microelectrodes that we were lowering into the VIIIth nerve actually passed through the flocculus, and we were soon able to confirm Steve and Albert's findings. However, the lack of modulation of P-cell simple-spike activity when the animal fixated on a stationary target while being oscillated was puzzling to me—there was no obvious reason for it, and it meant that the flocculus was making little or no contribution to the *normal* VOR. Almost immediately, Jim Fuller and I found an explanation

for this: The simple spike activity of the P-cells also modulated when the *stationary* monkey tracked a moving target, as though the cells were encoding the velocity of the eyes as well as the velocity of the head. Remarkably, these eye and head signals had the same directional preference (discharges increasing with ipsilateral motion), were of roughly the same strength, and were summed algebraically, which meant that when the oscillating monkey fixated on a stationary target, so that its eye velocity was almost the same but opposite in direction to the head velocity, these two signals canceled one another, hence the lack of observed P-cell modulation. In effect, the P-cells were encoding gaze velocity, which was the velocity of the eyes with respect to the stationary surroundings and was given by the sum of the velocity of the head with respect to the surroundings and the velocity of the eyes with respect to the head.

One of the remarkable things about recording in the flocculus was that gaze velocity was encoded only in the discharges of the output cells—that is, the P-cells—and not in the many mossy fiber inputs to those P-cells, the discharge behavior of which generally resembled that of vestibular afferents (encoding angular head velocity) or oculomotor motoneurons (encoding eye position and eye velocity) or neurons receiving visual inputs (encoding retinal slip velocity). Clearly, the P-cells were synthesizing the gaze velocity signal. Or perhaps they were encoding the velocity of the track target with respect to the surroundings, which would mean they were summing together three signals rather than two: the velocity of the head with respect to the surroundings ("head velocity"), the velocity of the eyes with respect to the head ("eye velocity"), and the velocity of the target with respect to the eyes ("retinal slip velocity"). Note that target velocity is also given by the sum of gaze velocity and retinal slip velocity. Jim Fuller and I published a preliminary report of our findings, proposing that the simple spike discharges of the P-cells in the monkey's flocculus were effectively encoding target velocity (Miles and Fuller, 1975), and I incorporated this into a signal flow model of the open-loop VOR and the negative feedback ocular pursuit system (Miles, 1976, 1977). In our experiments, the retinal slip velocity was mostly rather small so that a visual contribution to P-cell discharges was generally minor if not negligible (less than 5 percent), and we subsequently came to refer to them as gaze velocity P-cells.

The existence of eye velocity signals in flocculus P-cell discharges complicated our plans to investigate the neurophysiological basis of the adaptive changes in VOR gain; the problem is best appreciated from Figure 1, which shows our signal flow model of the VOR incorporating the gaze velocity P-cells in the flocculus (bounded by the dashed line). We considered the head velocity input to the P-cell to be a vestibular feedforward signal and the eye velocity input to be an efference copy signal in a positive feedback loop. Robinson and others had long incorporated such internal positive feedback loops in their models of the primate ocular pursuit system. The boxes A,

B, C, and D in Figure 1 represent the potential gain elements that might mediate the adaptive changes in VOR gain. The gain of the VOR could be increased, for example, by a decrease in the gain of element A (as hypothesized by Ito) and/or by an increase in the gains of elements C, D, or B. We examined the effect of long-term changes in VOR gain on the gaze velocity P-cells in the monkey's flocculus, evaluating the strength of the head velocity signals carried by the P-cells using Steve and Albert's paradigm of oscillating the animal while it fixated a target moving with the chair. We also evaluated the strength of the eye velocity signals carried by the P-cells by having the stationary monkey pursue a moving target. Our major finding was that in monkeys with high VOR gain following exposure to $\times 2$ spectacles, the gaze velocity P-cell discharges were significantly more sensitive to head velocity than to eye velocity. In fact, the increase in the sensitivity to head velocity roughly matched the increase in the VOR gain. This meant that during oscillation in the dark, the elevated head velocity signal roughly canceled the now elevated eye velocity signal and P-cell modulation continued to be minor (i.e., the flocculus continued to make only a minor contribution to the VOR in the gain-changed monkey). In the model in Figure 1, such differences in the monkeys with high VOR gain could have resulted from an increase in the gain of elements A and/or C. If the increased sensitivity of the P-cells to head velocity were due solely to an increase in the gain of element A in the flocculus, then this would have operated to decrease VOR gain and it would be necessary to invoke an additional change (increase) in the gain of element D to achieve the necessary increase in the VOR gain. Further, element D, which is in the brain stem, would be properly regarded as the modifiable element subserving the VOR gain increase. We concluded that the modifiable elements mediating the increase in VOR gain were in the brain-stem vestibular pathways, and are represented in Figure 1 by elements C and/or D.

Our findings were published in a back-to-back sequence of four papers. The first paper described the effects of telescopic spectacles on VOR gain (Miles and Eighmy, 1980). The second described the VIIIth nerve recordings in normal and gain-changed monkeys, essentially reporting no differences

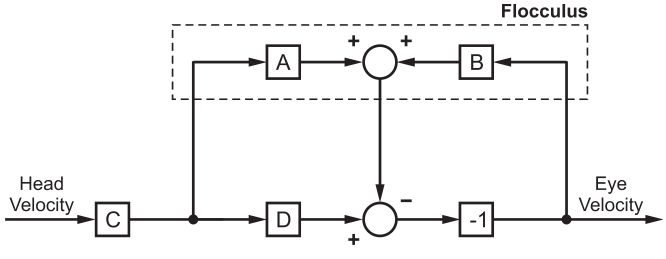

Fig. 1. Signal flow model of the gaze velocity P-cells in the flocculus.

(Miles and Braitman, 1980). The third described the discharge characteristics of neurons in the flocculus of normal monkeys (Miles, Fuller, Braitman, and Dow, 1980). The fourth described the discharge characteristics of P-cells in the flocculus of gain-changed monkeys and concluded that the synapses responsible for adaptive gain control were in the brain stem (Miles, Braitman, and Dow, 1980). Data collection had taken several years, and the quantitative data analysis took more than another year—the computers available at that time were quite slow and the quantitative data analysis was very labor intensive. Jim Fuller had left my lab soon after this project began, and I had been joined by another postdoctoral fellow, David Braitman, as well as a visiting scientist, Bruce Dow, both of whom made valuable contributions. Beverley Eighmy worked as a technician in the lab and also helped with some of the data analysis. In the last of the four papers, we ended by pointing out that, during the initial exposure to the telescopic spectacles, the discharges of the gaze velocity P-cells would reflect the VOR gain error and so might be responsible for the induction of the long-term changes in synaptic transmission in brain-stem vestibular pathways that we were convinced mediated the changes in VOR gain. This idea was taken up by Steve Lisberger, who had recently joined me as a postdoctoral fellow. Steve rewarded monkeys for fixating on a small target presented against otherwise dark surroundings while the monkey and the target were moved either in phase or 180 degrees out of phase to mimic the gaze velocity events—and presumably also the P-cell discharge modulation—that normally occur when the monkey first wears minifying or magnifying spectacles. This resulted in "adaptive" changes in the gain of the VOR even though there was no gross retinal image slip, consistent with the hypothesis that the error signal guiding recalibration of the VOR could be the modulation of gaze-velocity P-cell discharge (Miles and Lisberger, 1981a).

Steve also made another interesting finding. In the late 1970s, the visual backup to the VOR was generally studied by placing the stationary subject inside a cylindrical drum that rotated around the subject about a vertical axis. The inside walls of the drum were painted with black and white vertical stripes to provide a powerful visual stimulus. The heavy drum was first brought up to speed in the dark, then the lights were turned on for perhaps a minute and the subject's eye movements were recorded. These ocular responses consisted of tracking movements in the direction of drum rotation interrupted by resetting saccades, a pattern termed optokinetic nystagmus (OKN). The development of OKN over time had been well described by Cohen, Matsuo, and Raphan (1977) and generally showed two distinct phases that were felt to reflect two distinct mechanisms—an early component (OKNe) with brisk dynamics and a delayed component (OKNd) with sluggish dynamics. Steve found that changes in VOR gain were associated with parallel changes in the magnitude of OKNd, whereas OKNe was unchanged. This finding suggested that the modifiable elements responsible

for the VOR gain changes were located between the sites at which these two mechanisms gained access to the final oculomotor pathways (Lisberger, Miles, Optican, and Eighmy, 1981). The clear suggestion was that the variable gain element was shared by the VOR and OKNd. One possible advantage of such a shared arrangement was that the visual and vestibular control systems were synergistic, both working to compensate for rotational disturbances of the observer, and so would benefit from sharing the same coordinate framework and projection pathways. All of our new findings on VOR gain adaptation were summarized and discussed more fully in a review article (Miles and Lisberger, 1981b). Together with another postdoctoral fellow, Lance Optican, who had joined me from Johns Hopkins, we also showed that VOR gain adaptation could be frequency selective (Lisberger, Miles, and Optican, 1983), proposing an adaptive equalizer model of the primate VOR (Miles, Optican, and Lisberger, 1985) and, together with David Zee at Johns Hopkins, showed that bilateral ablation of the flocculus (and ventral paraflocculus) eliminated the adaptive capability of the VOR in monkeys (Lisberger, Miles, and Zee, 1984).

Those were the last projects that I did on the flocculus and plasticity of the VOR, and I never again recorded single units. Already by 1980 I felt that I had expended too much effort on this project—almost six years at that point. My contention that the synaptic modifications responsible for VOR gain adaptation were in the brain-stem vestibular pathways initially met with considerable skepticism. Others have since confirmed most of our findings regarding the changes in flocculus P-cell discharges with long-term changes in VOR gain (Lisberger, Pavelko, Bronte-Stewart, and Stone, 1994), and there is now good evidence for modifiable elements in brain-stem vestibular pathways (Lisberger, 1994; Lisberger, Pavelko, and Broussard, 1994; McElvain, Bagnall, Sakatos, and du Lac, 2010). Interestingly, new data suggest that the neural modifications underlying changes in VOR gain occur initially in the cerebellum but then shift to the brain stem during the subsequent consolidation process that marks an enduring (plastic) change (Kassardjian, Tan, Chung, Heskin, Peterson, and Broussard, 2005; Shutoh, Ohki, Kitazawa, Itohara, and Nagao, 2006).

The transfer of fixation between near and far objects involves changes in vergence eye movements and accommodation, each under separate visual feedback control but known to be cross linked in the brain. In a complete departure from my earlier work, Stuart Judge and I devised what we called laterally-displacing periscopic spectacles to increase or decrease the apparent separation of the two eyes—thereby increasing or decreasing the required amount of vergence per unit change in accommodation—and were able to show that the gains of the neural cross linkages between vergence and accommodation were subject to adaptive regulation (Judge and Miles, 1985).

In 1980, I moved to Bob Wurtz's new Laboratory of Sensorimotor Research in the National Eye Institute (NEI) intramural program at the

NIH and, having recently acquired U.S. citizenship, I was able to take up a permanent position. From my point of view, Bob was the ideal laboratory chief: once appointed you were left alone to get on with it. Bob also attracted a group of unusually talented scientists—including Mickey Goldberg, David L. Robinson, Lance Optican, Bruce Cumming, Ed FitzGibbon, and Okihide Hikosaka—and this made for a very lively intellectual environment. However, Bob's new lab was in a new building that was still some months away from completion, so I was temporarily without a lab. Stuart Judge had moved to Oxford some months before and kindly invited me to join him there to extend our previous study using rather more refined methodology. The NIH would permit me to work in Oxford for only a few months, so I was obliged to return to Bethesda before completing this study. Because my new lab was still not ready, I completed the study in David Robinson's lab at Johns Hopkins in early 1981, but it didn't get published until some years later, after Lance Optican had helped out with the data analysis (Miles, Judge, and Optican, 1987).

The Initial Ocular Following Response

It was now 1981, and for some time I had wanted to explore the visual—rather than vestibular—stabilization of gaze. Because I was now obliged to set up a new lab, this was an opportune time to make the change. The traditional way to study the visual stabilization of the eyes was with an OKN drum, and the assumed adequate stimulus here was simply global retinal slip. Given the complexities of normal visual experience, I did not see how such a crude global system could function in the real world and, working with a new postdoctoral fellow from Japan, Kenji Kawano, we soon discovered that indeed visual stabilization of the eyes was much more complicated than previously assumed. Instead of sitting inside an optokinetic drum, our monkeys faced a large flat screen onto which we back-projected a densely textured image that could be moved with servo-controlled mirror galvanometers. This gave us much more control over the composition of the visual stimulus as well as the onset, direction, and speed of its motion. We immediately found that brief motion ramps (velocity steps lasting 100 ms) elicited tracking movements of the eyes at ultra-short latencies—as short as 50 ms with optimal stimuli. We referred to this initial tracking as the ocular following response (OFR) and were mainly interested in the initial open-loop responses recorded within two reaction times of stimulus onset (100 ms). This meant that the measured responses were very small: the eyes simply cannot move very far in such a short time. In order to get good signal-to-noise, we had to record eye position with very high resolution—this meant using the electromagnetic search coil pioneered by Albert Fuchs and David Robinson—and we also had to average many responses, often more than 100. Fortunately, the initial OFR was very machine-like even though we

had neither trained the animals to track the movements nor reinforced them for doing so. That we were dealing with an automatic reflex became clear when the motion stimulus was a one-dimensional sine-wave grating. Remarkably, for a given contrast, latency was solely a function of the temporal frequency (the product of spatial frequency and speed), which specified the rate of change of luminance (in Hz) at any given point on the screen, and this suggested to us that the OFR was triggered by the local changes in luminance. Such direct dependence on the precise physical parameters of the visual stimulus was to become a hallmark of the initial OFR, indicating that it resulted from a rather direct link between the visual and oculomotor systems; although we were recording *motor responses*, the OFR would turn out to be a valuable source of information on the early cortical processing of the *visual motion stimulus*. However, our initial studies mostly indicated that the OFR had a number of special features that allowed it to deal with a variety of previously unforeseen real-world visual problems.

In exploring our environment, we use rapid saccadic eye movements to redirect our gaze from one object to another, thereby bringing images of potential interest into the region of the fovea where our vision is most acute. We found that these rapid shifts of gaze had a profound influence on the OFR. Motion applied to the scene in the immediate wake of a (centering) saccade generated a much better OFR than the same motion applied a few hundred milliseconds later. The magnitude of this transient *postsaccadic enhancement* was dependent on the retinal stimulation during the antecedent saccade, and a saccade-like shift of the visual background alone was sufficient to cause a similar transient enhancement of the OFR to a subsequent motion of that background. Interestingly, this *visual enhancement* did not show interocular transfer—saccade-like shifts seen by one eye did not enhance the OFR to motion seen by the other eye—indicating that the enhancement was occurring in the early part of the visual pathway, before the inputs from the two eyes converge.

From the functional point of view, this transient postsaccadic enhancement was most opportune because the eyes do not always come to a complete stop immediately after a saccade, often drifting onward or backward for 100 ms or more. These postsaccadic ocular drifts, termed glissades, which undermine retinal image stability and hence compromise visual acuity, occur when the brain fails to program the correct level of innervation to hold the eyes stationary in their newly acquired position. Lance Optican and I had earlier used persistent postsaccadic drifts of the visual background to show that there was a visually mediated adaptive mechanism working to minimize glissades, and we proposed a new pulse-slide-step model of saccadic innervation to explain our findings (Optican and Miles, 1985). Together with David Zee, Lance and I also showed that this adaptive mechanism was disabled by flocculus lesions (Optican, Zee, and Miles, 1986). In operating to stabilize the eyes with respect to the stationary environment, the OFR would work

to suppress any residual glissades, and the transient postsaccadic enhancement of the OFR would occur at the very time that ocular stability is most threatened by the glissades. Another important point is that such *transient* boosts in the gain of a negative-feedback control system avoid the overshoot and oscillation that can occur with *prolonged* increases in gain.

Partitioning the image on the screen into separate central and peripheral regions using two projection systems (and applying the OFR motion stimuli only when the animal looked at the center) showed that the visual enhancement of the OFR was local. Thus, a saccade-like shift applied to the central (or peripheral) retina enhanced the OFR to a *subsequent* motion in that same central (or peripheral) region. In contrast, a saccade-like shift applied to the peripheral retina caused a brief powerful *suppression* of the OFR to *concurrent* motion in the central retina. This *peripheral suppression* showed excellent interocular transfer: saccade-like shifts in the peripheral field of one eye suppressed the OFR generated by concurrent motion in the central field of the other eye. This indicated that the suppression must be occurring within the central nervous system (CNS) at a point receiving inputs from both eyes. From the functional point of view, this peripheral suppression would help to prevent the ocular following system from tracking the retinal image motion that occurs when saccadic eye movements sweep the eyes across the visual scene, a form of *saccadic suppression*. In fact, saccade-like shifts applied only to the center of the visual field actually elicit OFRs (albeit small and transient), whereas such movements applied to the periphery alone or to the whole field do not.

Partitioning the visual scene into separate central and peripheral regions also showed that en masse movement of the visual scene was not the optimal stimulus for the initial OFR. If the center was quite large (20° to 40° across), and the motion was again applied only when the animal looked at the very center, the *direction* of the OFR was always determined by the direction of the motion in the central region, regardless of the direction of motion in the surround. However, the latter had an anomalous effect on the *magnitude* of the OFR, which was actually *reduced* when the motion in the periphery was in the *same* direction as the motion at the center—en masse motion—and was *increased* when the motion in the periphery was in the *opposite* direction to that at the center. This anomalous effect of peripheral motion seemed to suggest that the OFR was optimized for tracking moving objects: a fixated object that suddenly starts moving to the right causes rightward motion of the images in the central retina and results in a rightward OFR so that the image of the stationary background in the peripheral retina would then be seen to move leftward. Note that the central image motion here is due to *afference* (stimulus motion) whereas the peripheral image motion is due to *reafference* (observer motion).

The large size of the central area required for this anomalous reafferent effect suggested that, under normal conditions, the objects that would

best engage the ocular following system would generally be stationary and nearby, their retinal images moving only because the observer was moving. Thus, the moving observer who attempts to fixate on nearby stationary objects must track them and will experience contrary afferent and reafferent motions in the central and peripheral retinas, respectively, resulting in optimal engagement of the ocular following system. The fact that reafferent motion in the periphery aided rather than impeded the visual tracking of the afferent motion at the center was not due to inversion of the sign of its visual input: motion in the periphery alone generated OFRs that were always in the direction of the seen motion (albeit weak). This led us to suggest a negative feedback tracking system *driven by afference* from foreground images moving in the central retina and *enhanced by reafferent* background images moving in the opposite direction in the peripheral retina (motion parallax). We termed this *positive reafferent modulation*.

The long-term adaptive regulation of VOR gain that I had studied earlier was deemed necessary because the VOR operated open-loop and was therefore very sensitive to fluctuations in internal parameters that might occur as a result of aging, trauma, disease, fatigue, and so forth. However, even closed-loop, negative-feedback mechanisms such as the OFR would have a preferred forward loop gain: if this gain were too high, the OFR would tend to display overshoot and oscillation, and if this gain were too low, the OFR would tend to show undershoot and large steady-state errors. We therefore sought to determine if the gain of the OFR was subject to visually mediated long-term adaptive regulation.

Our adaptation paradigm involved repeated exposure of the monkey to double-ramp motions ("velocity steps") of the visual scene. Each of these two ramps lasted only 150 ms, and they could differ in either speed ("speed steps") or direction ("direction steps") depending on the experiment. The idea was that the first ramp would initiate an OFR and the second would create a consistent error. For example, in a speed step, the second ramp could be faster or slower than the first, simulating under- or over-shoot, respectively. Over a period of hours, simulated undershoots caused gradual increases in the initial OFR, and simulated overshoots caused gradual decreases in the initial OFR. This adaptation was directionally selective so that in a given experiment it was possible to adapt vertical responses independently of horizontal, rightward independently of leftward, and upward independently of downward. Also, to some extent, this adaptation was speed dependent, whereby the initial OFR to *high-speed* stimuli could be adaptively increased (or decreased) while the initial OFR to *low-speed* stimuli was being adaptively decreased (or increased). In the direction-step paradigm, the second ramp was directed 90 degrees counterclockwise to the first, so that if the first ramp was rightward, then the second was upward and so on. This paradigm gradually brought out orthogonal responses to our 100-ms test ramps (e.g., the initial OFR to a rightward ramp now included

a substantial upward component). Thus, even the *direction* of the OFR was subject to adaptive regulation. Such versatile adaptive capabilities suggested to us that the OFR was well optimized and that its gain in each of the various directions was tuned to some optimal value.

Kenji Kawano returned to Japan in the summer of 1985 and our various findings on the monkey's OFR were published soon afterward (Kawano and Miles, 1986; Miles and Kawano, 1986; Miles, Kawano, and Optican, 1986). We concluded that, although the OFR operated as a reflex, it had many special features to deal with problems caused by various incidental factors such as saccades, glissades, and reafference, and its performance was optimized by a very versatile adaptive mechanism. Kenji continued to work on the OFR in monkeys and obtained strong evidence that the initial OFR was mediated by the medial superior temporal (MST) area of the cortex, a region known to be important for the processing of visual motion. Meanwhile, I was joined by a new postdoctoral fellow, Reuven Gellman, and together with a clinical fellow, Jim Carl, we recorded short-latency OFRs in humans, which we found to be very similar to those of monkeys. One particularly interesting finding was that when the initial OFRs to one-dimensional sinewave grating stimuli were normalized with respect to spatial frequency, every one of our subjects showed the same dependence on temporal frequency—bandpass characteristics with a peak at 16 Hz—indicating that temporal frequency rather than speed per se was the limiting factor over the entire range examined. This suggested that, in humans too, the underlying motion detectors were responding to the local changes in luminance (Gellman, Carl, and Miles, 1990).

Two new postdoctoral fellows joined me—Urs Schwarz from Switzerland and Hubert Kimmig from Germany—and we embarked on some new projects. Hubert did a very nice study on the effects of stationary textured backgrounds on the initiation of pursuit eye movements in monkeys (Kimmig, Miles, and Schwarz, 1992), while Urs set about trying to find evidence for a new vestibular response that we later called the translational vestibulo-ocular reflex (TVOR). In 1987–88, I had a year's leave of absence, which I spent at the City University of New York, working with Josh Wallman at City College. Josh had developed an exciting new model of myopia in the domestic chick, and we did a series of experiments that showed that persistent near viewing in the upper visual field could result in local myopia in that part of the visual field (Miles and Wallman, 1990). I returned to Bethesda in early 1988 and resumed experiments on the hypothesized TVOR with Urs Schwarz.

Translational Disturbances of the Observer and of the Visual Scene

Our finding that the initial OFR was subject to positive reafferent modulation indicated that the OFR had some special features associated with translational—rather than rotational—disturbances of the observer. This

led me to think about the optic flow experienced by the observer who undergoes lateral (sideways) translation, and I began to wonder if there was a VOR that compensated for such motion. I knew that the conventional VOR compensated solely for *rotations* of the head (let us call it the RVOR) and that it relied on inputs from the semicircular canals in the labyrinth, which Goldberg and Fernandez (1975) had shown were selectively sensitive to angular accelerations and insensitive to linear accelerations. However, Goldberg and Fernandez's paper had also shown that the otolith organs in the labyrinth were selectively sensitive to linear accelerations and insensitive to angular accelerations, and this led me to wonder if the otoliths might support a second VOR that compensated for lateral *translations* (let us call it the TVOR). A problem here was that lateral translation of the observer causes complex image shear because the nearby objects move across the field of view more rapidly than the distant ones (motion parallax), and a given compensatory eye movement can only eliminate the retinal image motion of objects stationed at a particular viewing distance. Given that primates had frontal vision, vergence eye movements, and stereopsis, it seemed to me that the challenge facing the TVOR during lateral translation would be to stabilize binocular gaze on the depth plane containing the object of regard. To be optimally effective, therefore, the gain of this hypothetical TVOR would have to be inversely proportional to the viewing distance necessitating range-finding information, which I thought might be provided by the vergence angle between the two eyes and/or the accommodative effort used to focus the eyes on the object of regard.

A visit to the library failed to turn up clear evidence for a robust TVOR, and I thought this might have been because in previous studies the subjects had always been translated in darkness without any thought that viewing distance might be important. (Of course, subjects were in darkness to prevent them from using visual tracking.) Urs Schwarz and I recorded vergence and accommodation in stationary, fixating monkeys and found that after the fixation light was turned off—leaving them in darkness—the monkeys often retained the same vergence angle and the same level of accommodation for a few hundred milliseconds, sufficient time for us to translate the whole monkey briefly and record any associated TVOR. Urs and I improvised a linear sled driven by a servo motor from an old turntable and recorded the monkey's eye movements during brief (200-ms) lateral (sideways) accelerations along the interaural axis. The acceleration was applied only after the monkey had satisfactorily fixated a small target light located at one of several possible viewing distances and the target was extinguished just before the sled began to move, leaving the monkey in total darkness during the translation. We found that sled motion elicited robust compensatory eye movements that were a linear function of the inverse of the prior viewing distance and we attributed these responses to a TVOR. The modulation with viewing distance was less than required, so that the TVOR undercompensated with

near viewing and overcompensated with distant viewing, perhaps because the conditions were so impoverished (passive viewing in darkness).

At this point, I recalled our earlier suggestion that the OKNd provided a visual backup to the RVOR and shared the neural pathway containing the gain element responsible for adaptive gain control of the RVOR. It occurred to me that the OFR—with its special sensitivity to motion parallax—might provide a visual backup to the TVOR and, if so, might share its dependence on viewing distance. At the beginning of 1989, a new postdoctoral fellow, Claudio Busettini, joined me from Italy, and together we sought to find out if the OFR was sensitive to the viewing distance. We seated the monkey in a chair mounted on a rail, and this allowed us to adjust the viewing distance to the screen onto which the OFR stimulus was back-projected. Of course, the size and speed of the back-projected image also had to be adjusted so as to preserve a constant motion stimulus on the retina at all viewing distances. Even though the visual motion stimulus was always the same, we found that the amplitude of the initial OFR was inversely proportional to the viewing distance with a sensitivity comparable to that of the TVOR. This led us to propose two visuo-vestibular mechanisms, one dealing with rotational disturbances—the RVOR and OKNd—and the other with translational disturbances—the TVOR and OFR (Miles and Busettini, 1992; Schwarz, Busettini, and Miles, 1989). Using wedge prisms to dissociate the distance cues—vergence and accommodation—we found that neither of these cues alone (nor a linear combination of the two) could account entirely for the dependence on viewing distance of either the TVOR or the OFR. We therefore suggested that the important cue was *perceived distance*, a rather complex entity that was known to be influenced by many factors.

The data describing the dependence of the TVOR and the OFR on viewing distance were published in two back-to-back papers (Busettini, Miles, and Schwarz, 1991; Schwarz and Miles, 1991). The need for the dependence on viewing distance was clear for the TVOR but less obvious for the OFR, and at first, we assumed that it was perhaps simply tolerated by the OFR as the cost of sharing a pathway and a coordinate framework with the TVOR. However, we had known for some time that the dependence of the OFR on speed showed progressive saturation, and Claudio's new experiments showed that the saturation level was inversely related to the viewing distance, indicating that the saturation originated upstream of the elements whose gain modulated with viewing distance. This meant that, under normal viewing conditions, this speed saturation would tend to offset the dependence on viewing distance because the retinal slip speeds experienced by the moving observer tend to vary inversely with viewing distance, resulting in greater saturation with nearer viewing.

A later study by Geoffrey Bush, who did a postdoctoral fellowship with me in the early 1990s, showed that the vertical eye movements induced by

a brief period of free fall—the vertical TVOR—also had a gain inversely proportional to viewing distance, and these experiments provided an estimate of the response latency that was much shorter than any in the recent literature (Bush and Miles, 1996). These experiments were all done on monkeys, and subsequent studies on humans showed a similar (though weaker) TVOR; dependence on viewing distance was evident in the human OFR *only* when the visual and vestibular stimuli were interleaved so that, on any given trial, the subject did not know whether *he* would be moved—eliciting the TVOR—or the *visual image* would be moved—eliciting the OFR (Busettini, Miles, Schwarz, and Carl, 1994). It seems that the distance cues used by humans were even more complex and context specific than those used by monkeys.

I had one other postdoctoral fellow in the 1990s, Rich Krauzlis, who worked mostly independently. Rich came from Steve Lisberger's lab at University of California, San Francisco (UCSF) and was so competent and energetic that he simply forged ahead and managed very well with only minimal help from me. I have real regrets that I did not have more interaction with someone so capable, but, in any event, Rich did a very fine series of experiments on monkeys that dealt with the initiation of pursuit and saccades, including the role of the oculomotor vermis in this process, and he made very elegant use of the gap paradigm (Krauzlis and Miles, 1996a, b, c, d; Krauzlis and Miles, 1998; Krauzlis, Zivotofsky, and Miles, 1999).

The Initial Disparity Vergence Response

Vergence eye movements are used to align both eyes on the same object and so must vary with the viewing distance, nearer viewing requiring greater convergence. It had been known since the classic experiments of Rashbass and Westheimer in the early 1960s that the vergence eye movements responsible for binocular alignment depended in large part on the slight difference in the locations of the images on the two retinas due to the slight difference in the viewpoints of the two eyes (binocular disparity). It had also been suggested that vergence errors were sensed by disparity-selective neurons in the visual cortex: in the usual negative-feedback control models, neurons activated by images nearer than the plane of fixation (crossed disparities) caused increased convergence, and neurons activated by images beyond the plane of fixation (uncrossed disparities) caused decreased convergence.

Claudio Busettini and I found that, without training or reinforcement, small disparity steps applied to large textured patterns elicited consistent, machine-like, vergence eye movements that were always in the appropriate direction for a servomechanism that operates to correct residual vergence errors and, amazingly, had latencies of less than 60 ms in monkeys—less than half that previously reported with small fixation targets. For these

experiments, monkeys faced a tangent screen onto which two identical random-dot patterns were back-projected. Orthogonal polarizing filters in the two projection paths together with matching filters in front of the two eyes ensured that each eye saw only one of the two patterns, the positions of which were controlled by mirror galvanometers. At the start of each trial, the two patterns appeared exactly superimposed and then were suddenly separated, creating a horizontal or vertical disparity step that lasted 200 ms before the projected images were blanked. Because the latency of the disparity vergence response (DVR) was similar to that of the OFR, we were concerned that each eye might be tracking the apparent motion that it saw ("monocular OFR"), in which event these vergence responses would not have resulted from the neural processing of the binocular disparity per se.

That this was not the case was evident from three control experiments that all yielded appropriate vergence eye movements at short latency. In the first, the disparate images appeared only after a period of darkness, so there was no motion; in the second, a new pair of (disparate) random-dot patterns was substituted at the time the disparity was applied, so that again there were no motion stimuli; in the third, the whole disparity step was applied to one eye only, yet both eyes contributed to the vergence response—the one not seeing the step moving in the *opposite* direction to the motion step seen by the other eye. We therefore concluded that it was appropriate to refer to these eye movements as disparity vergence responses.

Like the initial OFR, the initial DVR showed transient postsaccadic enhancement, whereby small disparity steps applied in the immediate wake of a centering saccade yielded vergence eye movements with much higher initial accelerations than did the same steps applied a few hundred milliseconds later. This postsaccadic enhancement of the DVR was like the postsaccadic enhancement of the OFR in also being at least in part due to the visual stimulation associated with the prior saccade. Thus, the DVR was subject to transient *visual enhancement* when the disparity steps were applied in the wake of conjugate (saccade-like) shifts of the textured pattern. From the functional viewpoint, we argued that this transient postsaccadic enhancement would help speed the binocular realignment of the eyes when gaze was shifted to new depth locations. These first experiments on the short-latency DVR of the monkey were published in 1996 (Busettini, Miles, and Krauzlis, 1996), and a subsequent study uncovered very similar responses in humans at only slightly longer latencies (Busettini, FitzGibbon, and Miles, 2001).

At Oxford, Bruce Cumming and Andrew Parker had made the nice observation that disparity selective neurons in the monkey's visual cortex were sensitive to the disparity of dense *anticorrelated* patterns (in which each black dot seen by one eye is matched to a white dot in the other eye), and the associated disparity tuning curves were often inverted compared with those obtained with the more usual *correlated* patterns (Cumming and Parker, 1997). These inverted tuning curves were consistent with early spatial

filtering of the monocular visual inputs prior to their binocular combination as in the disparity-energy model of the complex cells in striate cortex (Ohzawa, DeAngelis, and Freeman, 1990). Importantly, these dense anticorrelated patterns were perceptually rivalrous and lacked consistent depth (Cogan, Lomakin, and Rossi, 1993). Claudio and I were joined by Guillaume Masson from France and, working on monkeys and humans, we were able to show that small disparity steps applied to dense anticorrelated patterns gave rise to inverted (anticompensatory) DVRs (Masson, Busettini, and Miles, 1997). This indicated that the DVR derived its binocular information from an early stage of cortical processing, prior to the level at which depth percepts were elaborated, and relied upon neurons such as those recorded in the monkey's striate cortex by Cumming and Parker.

The Ocular Following Response: Dependence on Absolute Binocular Disparity

After developing the idea that the OFR worked in synergy with the TVOR to selectively stabilize images in the plane of fixation during lateral (sideways) disturbances of the observer, it occurred to me that, ideally, the OFR should be able to ignore the motion of objects that were nearer or more distant than the object of regard (i.e., ignore moving images that had binocular disparity). This led us to examine the effect of binocular disparity on the initial open-loop OFR. For this, subjects faced a tangent screen onto which two identical random-dot patterns were back-projected. Orthogonal polarizing filters in the two projection paths, together with matching filters in front of the two eyes, ensured that each eye saw only one of the two patterns, the positions of which were controlled by mirror galvanometers. The binocular visual stimulus now used to apply the disparity and elicit the OFR consisted of a horizontal step-ramp. The step was *disconjugate* (i.e., one eye saw a rightward step and the other a leftward step), serving to immediately position the binocular image of the random-dot patterns in a new depth plane nearer or farther than the screen, hence giving the patterns binocular disparity; the ramp was *conjugate* (i.e., the two eyes saw motion in the same direction, rightward or leftward, for 200 ms) and served to elicit an OFR. By applying the disparity at the last possible moment—at the start of the OFR stimulus ramp—we were able to avoid significant DVRs until the OFR was well underway. With this approach, binocular disparity attenuated the OFR substantially, just as we had hypothesized.

Claudio, Guillaume, and I published this finding in *Nature*, citing it as evidence that the OFR responded selectively to images in the plane of fixation with zero binocular disparity (Busettini, Masson, and Miles, 1996). However, two or three years later, after Claudio and Guillaume had left my lab, I realized that the attenuation of the OFR caused by the disparity step probably had nothing to do with its disparity. Embarrassingly, I had

forgotten that Kenji Kawano and I had shown some years earlier that a saccade-like shift of the image on the screen caused transient suppression of the OFR to concurrent motion (peripheral suppression). Working with a new postdoctoral fellow, Dongsheng Yang, I soon found that when the disconjugate step in our step-ramp paradigm was replaced with a conjugate one—so that both eyes saw the same rightward or leftward step and hence there was no change in the disparity of the pattern—the OFR elicited by the conjugate ramp was still attenuated. Clearly, a change in disparity was not required, and the attenuation of the OFR by the disparity step in our original experiments had actually been due to peripheral suppression.

I called Claudio and Guillaume to give them the bad news. Fortunately, I also had good news for them. It had occurred to me that applying the disparity and the motion uniformly to the whole screen image effectively simulated the visual experience of a rotating observer who is compensating only partially for the rotation, and who has a vergence error. However, our interest was in the observer who undergoes linear translation in a world with three-dimensional structure and who has visual stabilization mechanisms that utilize binocular disparity to distinguish objects moving in the plane of fixation (afference) from objects moving in other depth planes due to motion parallax (reafference). It occurred to me that the OFR might be much more complex than we had assumed, and that it might require a much more realistic test of our disparity hypothesis necessitating more complicated visual images that simulated afferent and reafferent motion.

Dongsheng and I therefore recorded the initial OFR elicited when the random-dot pattern on the screen was partitioned into horizontal strips that suddenly underwent motion, alternate ones leftward and rightward. Not surprisingly, with alternate strips undergoing conflicting motion, the initial OFR was very weak. However, we thought that if we could apply horizontal disparity selectively to alternate strips, say, to all those with leftward motion, then if our hypothesis were correct those ("reafferent") strips should lose their influence and the OFR would now be rightward, that is, dominated by the motion in the ("afferent") strips whose images were still in the plane of fixation. However, we still had the problem of introducing the disparity without eliciting peripheral suppression. In the original experiments, we had applied the step-ramp 50 ms after a centering saccade (to take advantage of postsaccadic enhancement), and Dongsheng and I now found that steps applied *during* the centering saccade—regardless of whether conjugate or disconjugate—lost almost all of their attenuating effect on the OFR to a conjugate ramp. This meant that we could "hide" the disparity step inside a saccade and thereby avoid peripheral suppression. Thus, in our new experiment, the disparity steps were applied during centering saccades and the conflicting motions commenced 50 ms after the saccades ended (thereby taking advantage of postsaccadic enhancement). The data were exactly in accordance with our hypothesis, indicating that the

OFR was sensitive to binocular disparity and strongly favored image motion in the plane of fixation. Furthermore, the OFR used disparity to distinguish afferent from reafferent motion; spatial location (central versus peripheral) was of secondary importance.

Claudio and Guillaume eagerly returned to Bethesda to complete the study, and we included additional experiments in which the conflicting motions commenced at various times after the centering saccade. This showed that the attenuating effect of the disparity was fully developed at the earliest time tested—10 ms after the saccade—too soon to be explained by a shift of attention, for example. The new data from our revised experiments were presented at the Festschrift for Han Collewijn in 2000 and were published the following year (Masson, Busettini, Yang, and Miles, 2001). This whole unfortunate episode indicated that we had seriously underestimated the complexity of our reflex responses.

That the OFR was sensitive to binocular disparity only when applied differentially to regions undergoing conflicting motion and not when applied uniformly to the whole screen image led us to think that the motion detectors driving OFR might be sensitive to *relative* disparity rather than *absolute* disparity. Note that absolute disparity refers to the slight differences in the positions of the two retinal images of a given object due to the differing viewpoints of the two eyes, whereas relative disparity refers to the differences in the absolute disparities of different objects within the visual scene due to differences in their distance to the observer. We already knew from the work of Regan, Erkelens, Collewijn, and others that human stereopsis (depth perceived from binocular disparity) was much more sensitive to relative disparity than to absolute. To obtain definitive evidence for relative disparity, it was necessary to show that the disparity tuning in one region of the visual field was dependent on the disparity in another region. Dongsheng Yang and I later used the same partitioned display of alternating strips with conflicting motion and found that the zero absolute disparity at which one set of strips had their maximal impact on OFR was not affected by changing the absolute disparity of the other set of strips with conflicting motion; that is, the responses to the two stimuli were separable. Hence, it was the absolute and not the relative disparity of the motion stimuli that determined their impact on OFR (Yang and Miles, 2003). This meant that the OFR selectively stabilized the retinal images of objects in and around the plane of fixation and so worked in harmony with the DVR, which had long been known to use absolute disparity to bring objects of interest into the plane of fixation.

The Initial Radial Flow Vergence Response

By 1997, there had been many papers in the literature concerned with the optic flow experienced by the moving observer and, in particular, with the

radial pattern of flow experienced by the moving observer who looks ahead. The streaming retinal images were seen as a rich source of information about the observer's rate of progress and direction of heading. It occurred to me that in order to maintain binocular alignment on objects of interest that lie ahead, the moving observer must continuously adjust the vergence angle between the two eyes, and I wondered if, in addition to binocular disparity, the vergence system might also utilize the radial optic flow. I had in mind that briefly presented large-field radial optic flow might elicit short-latency vergence responses. In particular, I wondered if brief *centrifugal* flow, in which retinal images flowed away from the fovea (simulating the observer's forward approach) might *increase* the convergence of the eyes and the reverse pattern of *centripetal* flow (simulating the observer's retreat) might *decrease* the convergence.

For technical reasons, we decided to try single steps of optic flow, using two slide projectors and switching between them so that the subject first saw a stationary random-dot pattern, and this was then suddenly replaced by a second one that was identical except slightly larger (producing a radial-flow step with a focus of expansion at the fovea) or slightly smaller (producing a radial-flow step with a focus of contraction at the fovea). As usual, we applied the simulated flow step in the immediate wake of a centering saccade. Using ourselves and a volunteer as subjects, Claudio, Guillaume, and I found that centrifugal steps resulted in increased convergence and centripetal steps resulted in decreased convergence. Latencies were again ultra-short (about 80 ms). These initial experiments simulated a change in viewing distance and so included size changes as well as radial flow. However, eliminating the change in size was without effect, and size changes applied alone, without radial flow, were ineffective. We felt that these initial vergence eye movements represented a binocular response to the radial pattern of optic flow but were concerned that they might have resulted from monocular tracking, each eye tracking the motion that it saw *in the nasal hemifields*. For example, with centrifugal flow there would be a net motion vector toward the nose in both nasal hemifields, and if each eye independently tracked that motion, the result would be increased convergence. Masking off different parts of the flow fields seen by each eye indicated that this was not the correct explanation. Thus, the binocular vergence responses to radial-flow steps persisted during monocular viewing and, importantly, also persisted when both nasal hemifields were masked off. In this latter case, each eye actually moved in the opposite direction to the net motion vector that it saw (in its temporal hemifield). We concluded that the vergence responses resulted from a true parsing of the radial flow pattern and so referred to them as radial flow vergence responses (RFVRs).

After we had published our initial study of the RFVR (Busettini, Masson, and Miles, 1997), I realized that as an observer moves forward or

backward the vergence angle between her two eyes must change at a rate that is inversely proportional to the square of the viewing distance in order to maintain binocular alignment on the object of regard. This meant that the RFVR might create a problem for an observer moving forward through a visually cluttered environment such as a forest: any convergence resulting from the optic flow created by the nearby trees would be inappropriate if the observer was trying to fixate on something far ahead.

Interestingly, Paige and Tomko (1991) had shown that there was a fore-aft TVOR that operated in complete darkness, working to increase the vergence angle during forward motion and reduce it during backward motion, and they also reported that the magnitude of these vergence responses increased with the vergence angle. (Though whether these TVOR responses were proportional to the square of the vergence angle, as required for full compensation, was not clear because Paige and Tomko had only a limited data set and had not attempted to fit such a function to their data.) However, I now began to wonder if the RFVR might provide a visual backup to this fore-aft TVOR in the same way that we had proposed that the OFR provided visual backup to the lateral TVOR. If so, the RFVR might share a pathway with the fore-aft TVOR and perhaps even share its dependence on viewing distance so that, under normal conditions, the RFVR would be severely attenuated with distant viewing, an effect that would help to reduce the impact of nearby visual clutter when the moving observer looked far ahead.

Dongsheng Yang and I, along with an ophthalmologist at the NEI, Ed FitzGibbon, decided to investigate the possibility that the RFVR was dependent on the viewing distance (or, more particularly, on the vergence angle between the two eyes). Using ourselves and volunteers as subjects, we faced a large tangent screen onto which two identical random-dot patterns were back-projected in exact register. A system of crossed polarizers and matching filters in front of the eyes ensured that each eye saw only one of the patterns, creating a single binocular image in the plane of the screen. These two projected patterns were then slowly separated horizontally, using mirror galvanometers, thereby adjusting the subject's vergence angle to the desired level for that trial. Once this desired vergence position had been reached, the two patterns were instantly replaced with two new ones that were 4 percent larger (or smaller), so that each eye saw a radial-flow step with a focus of expansion (or contraction) centered on the fovea. Thus, the radial flow steps were always of the same magnitude, but the subject's vergence angle varied from trial to trial. This revealed that the amplitude of the initial RFVR was proportional to the preexisting vergence angle and, hence, would be inversely proportional to the viewing distance under normal viewing conditions. We argued that this might reflect a shared pathway with the fore-aft TVOR and would help the moving observer to fixate on objects far ahead while passing through a visually cluttered area (Yang, FitzGibbon, and Miles, 1999). It seemed likely that dependence on the vergence angle

might represent a good compromise—if the gain of the RFVR were dependent on the *square* of the vergence angle, it might become unstable with near viewing.

The Disparity Vergence Response: Evidence for True Population Coding in the Medial Superior Temporal Area

The coding of information by the activity of populations of neurons has received considerable attention in recent years. In most cases, the so-called population coding referred to mechanisms whereby the aggregate activity of neurons with broad, overlapping tuning functions could achieve a finer representation of a particular sensory or motor function. However, in the study I am now going to discuss, the population activity conveyed information that was not evident at the level of the individual neurons, analogous to the way that words convey information that is not evident at the level of the individual letters. In this case, the information is an emergent property of the population activity and therefore truly deserving of the description, *population coding*. The neuronal recordings in question were carried out in Kenji Kawano's lab in Japan by two of his students, Aya Takemura and Yuka Inoue. I had continued to collaborate with Kenji, regularly visiting his laboratory in Tsukuba, which had been recording the activity in the MST area of the monkey's cortex associated with the initial OFRs elicited by conjugate velocity steps and the initial DVRs elicited by disparity position steps. For the latter, they constructed disparity tuning curves describing the dependence of the neuronal activity and the associated DVRs on the direction and magnitude of the disparity steps. They used anticorrelated as well as correlated random dot patterns and found that the disparity tuning curves for the DVRs were similar to those that we had described in humans, resembling the derivative of a Gaussian and well fit by Gabor functions. The disparity tuning curves of the single neurons in MST, however, were much more variable.

When Aya had finished recording, she sent the data to me in Bethesda, and we both agreed that it was extremely difficult to classify the neuronal tuning curves rigorously. Lance Optican suggested that we show the data to his postdoctoral fellow, Christian Quaia, a bioengineer from Italy, to see if he could help with this. Christian did a brilliant post hoc analysis of the data. He first fitted each neuron's disparity tuning curve to the disparity tuning curve for the associated DVR (with gain and offset the only free parameters). The goodness of these fits was then assessed by computing the fraction of the disparity-induced variation accounted for by the fits (r^2). This revealed that there were a few neurons with tuning curves that fit the tuning curve for the DVR reasonably well ($r^2 > 0.8$) with *either* correlated *or* anticorrelated stimuli; but none of the neurons had tuning curves that gave good fits with *both* types of stimuli. Thus, the goodness of the

fit depended on the *type of stimulus* used to generate the DVR, indicating that there were *no pure vergence-encoding cells*. Most remarkably, however, when Christian took the disparity tuning curves of all of the cells obtained from a given monkey and simply summed them together (without manipulating any weights), the summed activity fit the tuning curve for the DVRs of that same monkey extremely well ($r^2>0.93$). This was true for the unit data obtained with correlated and anticorrelated stimuli.

For the two animals from which most of the data were obtained, the shapes of the disparity tuning curves for the DVRs obtained with correlated stimuli were very similar for the two animals, but the shapes of the disparity tuning curves for the DVRs obtained with anticorrelated stimuli differed significantly for the two animals. These differences in the vergence data obtained with anticorrelated stimuli were such that the summed neural activity from one monkey gave a very poor fit to the vergence data obtained from the other monkey and vice versa ($r^2<0.35$). Thus, the summed neural activity for a given animal matched *only the DVRs of that same animal*, indicating that the neuronal population data reproduced the idiosyncrasies of the DVRs of the two monkeys.

Christian also used a fuzzy clustering algorithm to rank order the neurons objectively on the basis of the shapes of their tuning curves and, using a genetic algorithm, obtained strong evidence that the encoding of vergence in the population activity depended on contributions from across the entire range of tuning curves found among the disparity-selective cells in MST. Thus, the population code depended crucially on the aggregate activity of a heterogeneous collection of cells. In a subsequent analysis, Christian showed that the summed neuronal discharges also encoded the time course as well as the magnitude and direction of the vergence eye movements, indicating that the summed activity provided a complete description of the vergence motor output. In my view, the paper describing these data (Takemura, Inoue, Kawano, Quaia, and Miles, 2001) is one of the most compelling of all those purporting to describe population coding.

I think that the stimulus set that Aya and Yuka used had a number of features, some novel, that, in retrospect, were crucial for revealing the population coding in the MST area. First, they sought only to identify the possible contributions of the cells, individually and collectively, to one particular well-defined behavior—the DVR. Thus, they ignored the possibility that these cells discharged in relation to other stimuli and/or motor responses. In particular, they did *not* use an extensive set of stimulus parameters as others have often done in hopes of identifying the stimuli "preferred" by the individual cells. Second, their stimulus set extended well beyond the biologically useful (servo) range. It was the responses to the outlying stimuli that gave the tuning curves their *individual shapes*, and hence their individual identities. Third, they included stimuli—anticorrelated patterns—that are rarely, if ever, encountered in the real world and that elicit reversed vergence

responses with idiosyncratic features. That these subject-specific features of the motor responses were captured by the aggregate neuronal responses helped to persuade us that the population coding had genuine biological significance and was not simply a fortuitous epiphenomenon.

The Need for Better Control of the Visual Stimulus

In 2001, I did an experiment with Guillaume and Dongsheng that was based on some earlier psychophysical findings. Anstis and others had earlier reported that the perceived motion associated with step displacements (*phi motion*) could be reversed by reversing contrast during the step (*reversed phi*), and we now showed that the OFRs elicited by small step displacements could also be reversed by reversing the contrast during the step (Masson, Yang, and Miles, 2002). It was generally thought that Anstis's reversed phi (and, we assumed, our "reversed OFR") was mediated by dedicated low-level motion detectors that functioned without regard to form or perceptual features. Many computational models of this process had been suggested, and the so-called motion-energy model of Adelson and Bergen (1985) had been particularly influential. In the same way that Hubel and Wiesel had developed the idea that neurons in striate cortex sensed spatial orientation by operating as spatial filters oriented in *x-y space* and tuned for spatial frequency, Adelson and Bergen (and others) developed the idea that motion was sensed by spatiotemporal filters that were oriented in *x-t space* and tuned for spatial frequency. Such models were critically sensitive to the Fourier composition of the motion stimulus and responded to the motion energy, which was defined by the luminance modulation. However, it was possible to design moving stimuli that lacked motion energy—being defined not by luminance but by contrast, disparity, or flicker, for example—and so were invisible to these low-level motion sensors. Yet human observers had no problem perceiving the motion of such stimuli. This led to the idea that there were (at least) two motion-sensing systems, variously referred to as "energy-based" versus "feature-based," "first-order" versus "second-order," and "Fourier" versus "non-Fourier."

There was a very extensive psychophysical literature on this topic that had generated lots of interesting ideas about the neural processing of visual motion (and also binocular disparity), and I was keen to explore these ideas using our short-latency eye movements as a probe. I felt that the OFR, RFVR, and DVR could be used to investigate these visual processes objectively and quantitatively but only if we had much better control of the Fourier composition of our visual stimuli. Eventually, in 2003, I decided to drop the slide-projection approach that we had been using up to that point and develop a large-screen video display. Actually, we put together three displays, two in a Wheatstone stereoscope arrangement to provide the dichoptic stimuli required for the DVR and a third, stand-alone screen, directly ahead of the subject for exploring the OFR and the RFVR.

Many technical issues had to be addressed, requiring a detailed knowledge of personal computer (PC) architecture, graphics cards, video monitors, software, and so forth. The complete makeover of the lab took almost a year and involved seemingly endless calibrations and fine adjustments. For the design, construction, and testing, I relied heavily on my two coworkers, Boris Sheliga, who was a scientist from Russia, and Ed FitzGibbon, who was an ophthalmologist in the NEI. Our new setup was designed for human subjects only and allowed us to specify the harmonic composition of our visual stimuli in exquisite spatiotemporal detail. It was to make the final years of my research (2004–10) among the most interesting and productive of my career. Boris was a crucial part of all of this, taking care of the day-to-day running of the laboratory—including writing all of the software needed to generate the stimuli and to collect and analyze the data—and we worked very closely together right up to the time of my retirement.

Evidence for Energy-Based Sensing Mechanisms

The idea for the first experiment with our new approach came from reading Adelson and Bergen's lovely review. They had mentioned an apparent motion stimulus that I will refer to as the missing fundamental (*mf*) stimulus, which consisted of a square-wave grating that lacked the fundamental (see Figure 2A). When seen through a fixed window and moved smoothly, the *mf* stimulus was perceived to move in the direction of motion—nothing surprising about that—but when moved in discrete, quarter-wavelength steps, then it was generally perceived to move in the *opposite* direction to its actual motion. The explanation offered was that the first-order motion detectors responsible for the perception here were not sensing the motion of the raw images (or their features) but rather a spatially filtered version of the images, so that the perceived motion depended critically on the Fourier composition of the spatial stimulus. In the frequency domain, a pure square wave is composed entirely of the odd harmonics—first, third, fifth, seventh, and so on—with progressively decreasing amplitudes such that the third, fifth, seventh, and so on have amplitudes that are one-third, one-fifth, one-seventh, and so on, that of the first (i.e., the amplitude of the ith harmonic is proportional to $1/i$). The *mf* stimulus lacked the first harmonic and so was composed entirely of the remaining odd harmonics, with the third having the lowest spatial frequency and the largest amplitude. This meant that when the *mf* stimulus grating stepped one-quarter of its wavelength, the largest Fourier component, the third harmonic, stepped three-quarters of its wavelength in the forward direction. However, a *three-quarter-wavelength forward step* of a sine wave is exactly equivalent to a *one-quarter-wavelength backward step* and, because the brain gives greatest weight to the nearest neighbor image matches (spatial aliasing), the perceived motion was invariably in the *backward* direction. In fact, with

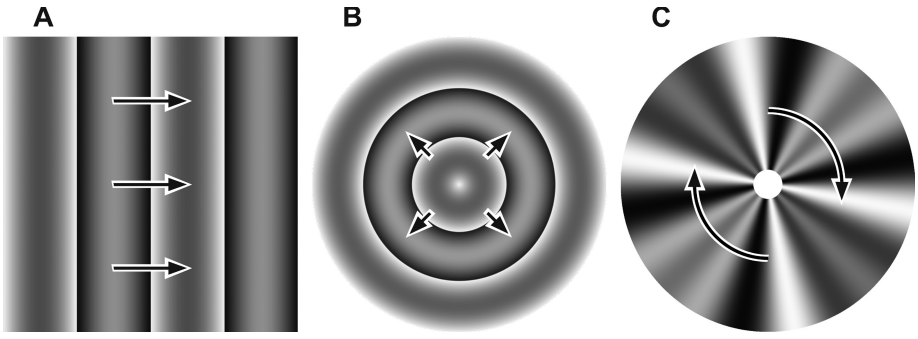

Fig. 2. Sample patterns used to generate optic flow. (A) A pattern of vertical bars for which the horizontal luminance modulation is that of a square wave lacking the fundamental; arrows indicate a quarter-wavelength *right*ward displacement of the pattern, which generates a *left*ward OFR. (B) A pattern of concentric circles for which the radial luminance modulation is that of a square wave lacking the fundamental; arrows indicate a quarter-wavelength radial expansion of the pattern, which generates an RFVR that decreases convergence. (C) A radial pattern for which the angular luminance modulation is that of a 3*f*5*f* grating pattern; arrows indicate a quarter-wavelength clockwise step of the pattern that results in the 3*f* component undergoing a counterclockwise step one-quarter of its wavelength and the 5*f* component undergoing a clockwise step one-quarter of its wavelength.

one-quarter-wavelength steps of the *mf* stimulus, all of the $4n$–1 harmonics (where n is an integer), such as the third, seventh, eleventh, and so on, shift in the backward direction, whereas all of the $4n+1$ harmonics, such as the fifth, ninth, thirteenth, and so on, shift in the forward direction, and the most prominent harmonic—the third—generally dominates the motion percept. (I will come up with a more complete explanation for that later in this chapter.)

The important point was that the direction of perceived motion was determined by the principal Fourier component rather than the overall pattern. We found that the initial OFR elicited by quarter-wavelength steps applied to an *mf* stimulus such as that seen in Figure 2A had the usual ultrashort latency and was invariably in the opposite direction to the motion of the pattern. In fact, the initial OFR here was almost identical to that elicited when the same quarter-wavelength steps were applied to a pure sine-wave grating whose spatial frequency and contrast matched that of the third harmonic (Sheliga, Chen, FitzGibbon, and Miles, 2005). As with the reversed OFR seen earlier with the reversed phi stimulus, the reversed OFR seen with the *mf* stimulus was consistent with the idea that the underlying motion detectors were energy-based rather than feature-based.

Soon afterward, we recorded the DVR elicited in human subjects when binocular disparities were applied to *mf* gratings using our new dichoptic viewing arrangement in which each eye saw its own video monitor through

a 45-degree mirror (Sheliga, FitzGibbon, and Miles, 2006). The *mf* patterns (again like those in Figure 2A) were identical at the two eyes except for a phase difference (i.e., binocular disparity) of one-quarter-wavelength, and this elicited a robust DVR with the usual ultra-short latency, that was always in the opposite direction to the disparity applied to the overall pattern (i.e., in the direction of the disparity of the principal Fourier component, the third harmonic). Thus, with an uncrossed disparity, for example, the DVR showed *increased* convergence, which as far as the overall pattern was concerned was *anticompensatory*. Like the anticompensatory DVR seen earlier with anticorrelated patterns, these new anticompensatory data supported the idea that the earliest DVR was a response to the disparity energy in the stimulus. While the RFVR and the OFR generated very different kinds of motor response and were elicited by completely different *global* patterns of optic flow, it seemed likely that both relied on the same low-level *local* motion detectors. We therefore sought to elicit RFVRs in human subjects by applying quarter–wavelength radial steps to concentric circular patterns where the radial luminance modulation was that of a square wave lacking the fundamental (see Figure 2B). While the overall pattern and the $4n+1$ harmonics (where n = integer) underwent radial expansion (or contraction), the $4n-1$ harmonics—including the principal Fourier component, the third harmonic—underwent the opposite radial motion. The radial motion commenced only after the subject had fixated on the center of the pattern so that the optic flow was centered on the fovea (i.e., centrifugal or centripetal optic flow pattern). For these experiments, we were joined by Yasushi Kodaka from Kenji Kawano's laboratory in Japan. We found that, as with the initial OFR, the initial RFVR was always in accordance with the motion of the third harmonic, consistent once more with mediation by motion detectors that were responding to the local motion energy (Kodaka, Sheliga, FitzGibbon, and Miles, 2007).

Nonlinear Interactions with Opponent Motion: Winner-Take-All

We were somewhat puzzled as to why the responses to the *mf* stimulus were always so completely dominated by the third harmonic, and it was not until we manipulated the contrasts of the individual harmonics that we understood what was going on. When the contrast of the third harmonic of the *mf* stimulus was *selectively* reduced below that of the next most prominent harmonic—the fifth, which moves in the opposite (forward) direction—then the OFR reversed direction and the third harmonic effectively lost *all* of its influence as the OFR was now dominated by the fifth harmonic. It was as though the principal Fourier component was actually suppressing the responses to the weaker competing harmonics and thereby dominating the OFR in a winner-take-all (WTA) fashion.

To examine this idea more carefully, we simplified things by using only two of the competing harmonics of the *mf* stimulus—the third and fifth—creating what we called a "3*f*5*f* pattern." When this 3*f*5*f* pattern underwent quarter-wavelength steps, there was opponent motion; the 3*f* component stepped *backward* one-quarter of its wavelength and the 5*f* component stepped *forward* one-quarter of its wavelength. (To further simplify the paradigm, we carefully selected a fundamental wavelength whose third and fifth harmonics were of equal efficacy when of equal contrast and presented singly.) These 3*f*5*f* stimuli indicated that the critical factor determining the OFR was the ratio of the contrasts of the two harmonics; when of similar contrast, both harmonics were effective and canceled one another so that the OFR was minimal, but when the two harmonics differed in contrast by more than about an octave (i.e., contrast ratio >2 or <0.5) then the one with the higher contrast completely dominated the OFR and the one with the lower contrast lost all of its influence: WTA (Sheliga, Kodaka, FitzGibbon, and Miles, 2006). This meant that the response to one grating was not independent of the response to the second grating (i.e., the system was nonlinear). Like others before us, we attributed such nonlinear interactions to mutual inhibition between the mechanisms sensing the motion of the competing harmonics. Amazingly, the nonlinear dependence on the contrast ratio was fully described (mean $r^2>0.99$) by a simple contrast-weighted-average model with only two free parameters.

Broadband and dual-grating stimuli had clearly uncovered significant nonlinearities in the visual information processing that could not have been seen with a single sine-wave stimulus. We felt that these nonlinear interactions favoring the component with the higher contrast also made functional sense: they would help to maintain binocular alignment selectively on the objects in the plane of regard because the retinal images of those objects would tend to be better focused—and hence tend to have higher contrasts—than the retinal images of objects in other depth planes. (To a first approximation, image blur operates like a low-pass spatial frequency filter.)

When 3*f*5*f* stimuli were used to elicit the DVR and the RFVR, these too displayed nonlinear interactions and generally showed WTA behavior (Kodaka, Sheliga, FitzGibbon, and Miles, 2007; Sheliga, FitzGibbon, and Miles, 2007). Once more, a difference in contrast of an octave or more was sufficient for the harmonic of higher contrast to dominate the RFVR and the vertical DVR, but it required more than a fourfold difference in contrast before the horizontal DVR displayed WTA behavior. Again, we attributed the nonlinear dependence on the contrast ratio to mutual inhibition between the detectors sensing the 3*f* and the 5*f* components, but this inhibitory coupling was clearly much weaker for the horizontal DVR. We are not sure why this is so. One might think that the mutual inhibition would have to be very powerful to be biologically useful, but if it were too strong, then the system would be very sensitive to even small differences in contrast,

rendering it unstable and overly sensitive to noise. Presumably, the strength of the inhibitory cross coupling is a compromise between the need for a clear winner and the need for noise immunity. Having a visual tracking mechanism operate initially to stabilize the most prominent harmonic might be more useful to the observer than having it respond to the average motion when no particular image is singled out for stabilization.

I was very interested in the spatial extent of the mutual inhibition postulated to be responsible for the WTA behavior and wanted to know what would happen if the competing harmonics did not occupy the same location (i.e., were not overlapping). But how could we separate the harmonics spatially if we had to use large-field stimuli to get our reflex mechanisms to respond? This led me to challenge our long-held belief that large-field stimuli were necessary to elicit our short-latency ocular responses and, to our amazement, we found that the horizontal OFR elicited by a vertical striped grating that occupied the full screen (30° high, 45° wide) was no greater than by a grating of the same contrast and spatial frequency that occupied only a narrow horizontal strip (1° high, 45° wide) at the screen center (Sheliga, FitzGibbon, and Miles, 2008a). Clearly, large-field stimuli were not necessary, and we soon found that the horizontal OFR elicited by horizontal 3*f*5*f* gratings still displayed clear WTA behavior when the pattern occupied only a narrow horizontal strip. Even more importantly, when the 3*f* and the 5*f* harmonics were restricted to *separate* horizontal strips, a vertical gap of one degree between them was sufficient to completely eliminate the nonlinear dependence of the OFR on their contrast ratio, and the OFR now approximated a simple vector sum of the responses to each grating strip alone. Thus, the nonlinear interactions responsible for the WTA outcome with the OFR were strictly local, indicating that the postulated inhibitory connections did not extend much beyond the (vertical) spatial confines of the visual stimuli.

Nonlinear Interactions with Component Motion: Global Normalization and Local Winner Take All

The OFR operates as a negative-feedback control system, and Kenji Kawano and I had shown some years earlier that it is subject to long-term, adaptive gain control, consistent with the idea that its gain is tuned to some optimal value. If an increase in the areal extent of the motion stimulus were to increase the visual input signal driving the OFR, it would have the same effect as raising the forward loop gain, potentially destabilizing the system. Ideally, the responses of an ocular tracking mechanism should be relatively insensitive to the spatial extent of the moving images. Such insensitivity to the size of the driving stimulus would require some sort of divisive normalization, a nonlinear process that has often been described in visual cortical neurons and attributed to mutual inhibition.

After we realized that a single narrow strip of grating was sufficient to elicit robust OFRs, we were keen to examine its spatial summation properties. For

this, we used a vertical stripe pattern (sinusoidal grating) that was partitioned into a number of horizontal strips each one-degree high and always equally spaced vertically (Sheliga, FitzGibbon, and Miles, 2008a). A single centered strip (covering 3.3 percent of the full screen) always elicited robust OFRs, and three strips (10 percent coverage) were sufficient to elicit the maximum OFR. Increasing the number of strips to 15 (50 percent coverage) had little impact—that is, responses had leveled off—and further increasing the coverage to 100 percent (full-screen image) actually *decreased* the OFR so that it was now often less than that elicited with only one strip. Thus, over a fivefold range (10–50 percent coverage), the initial horizontal OFR was independent of the total area of the stimulus. In this experiment, the gratings always had the same contrast, and in a second experiment, the contrast of the gratings could be fixed at one of four levels. The OFR showed essentially the same pattern of dependence on the number of strips (i.e., on the screen coverage) at any given contrast, but, significantly, the lower the contrast, the lower the magnitude at which the response leveled off. This indicated that the leveling off was *not* due simply to the passive achievement of some intrinsic upper limit in the magnitude of the tracking eye movement or the underlying motion signals ("ceiling effect"). Rather, this insensitivity to size over a fivefold range was seen as the result of an active process—divisive normalization—similar to that described by others in cortical neurons and attributed to global inhibition.

There were no competing motions in these last experiments: the motion all came from a vertical striped grating composed of a single sinusoid, albeit one broken up into separate horizontal strips that all moved together. In another study (Sheliga, Kodaka, FitzGibbon, and Miles, 2006), we used a vertical stripe grating pattern that consisted of two sine waves equivalent to the third and seventh harmonics of the *mf* stimulus, creating what we called a "3*f*7*f* pattern," which occupied the whole screen. Because both are $4n-1$ harmonics, with quarter-wavelength horizontal displacements of the 3*f*7*f* pattern, both harmonics underwent quarter-wavelength shifts in the same (backward) direction, here termed *component* motion. Again, when of similar contrast, both harmonics were effective; but when their contrasts differed by more than an octave, then the one with the higher contrast became dominant and the one with the lower contrast became ineffective: WTA. Thus, the WTA interaction between competing harmonics also applied to motion stimuli that shared the same direction and differed only in spatial frequency and speed.

In a subsequent study (Sheliga, FitzGibbon, and Miles, 2008b), the vertical striped pattern was composed of 3*f* and 7*f* gratings that were each confined to separate horizontal strips only one to two degrees high, and a robust WTA interaction was still apparent when the two gratings overlapped. However, unlike the situation with the *3f* and *5f* strips, when the *3f* and *7f* strips were separated by a vertical gap of up to eight degrees (the largest separation possible), the OFR was still less than the linear sum of the responses to each grating alone. We postulated that there were two nonlinear interactions operating here—*local* mutual inhibition resulting

in WTA behavior and *global* divisive inhibition resulting in normalization. Interestingly, motion stimuli with responses totally suppressed by coextensive opponent motion of higher contrast were rendered invisible to normalization, indicating that the local interactions responsible for the WTA behavior here were occurring at an earlier stage of neural processing than the global interactions responsible for the normalization.

Temporal Dynamics

A two-frame movie consisting of a single quarter-wavelength step applied to a sine-wave grating pattern occupying the whole screen was sufficient to generate robust, though transient, OFR, and introducing an inter-stimulus interval (ISI) of 10–200 ms (during which the screen was gray with the same mean luminance) reversed the direction of the initial OFR (Sheliga, Chen, FitzGibbon, and Miles, 2006). This reversal was reminiscent of the oft-reported reversal of perceived motion by brief ISIs, which had been attributed to the temporal dynamics of the early visual pathway and, in particular, to the negative phase of the well-known biphasic temporal impulse response function of the human visual system, reflecting the band-pass characteristics of its modulation transfer function. Interestingly, the RFVR could also be elicited with single radial steps, and brief ISIs resulted in reversal of the vergence response (Kodaka, Sheliga, FitzGibbon, and Miles, 2007).

These experiments with ISIs were all done under photopic luminance conditions and it has long been known that changing to scotopic conditions changes the human modulation transfer function from band-pass to low-pass in the frequency domain and from biphasic to monophasic in the time domain. We therefore repeated our experiments on the OFR in the dark-adapted subject using patterns with extremely low luminance. The changes were dramatic. I was the first subject and during the experiment protested that we were wasting our time because I was not able to perceive either the dim stimulus pattern or its motion. Fortunately, my colleagues insisted on finishing the experiment: The OFRs to quarter-wavelength steps in these dim conditions had longer latencies but were by far the largest that we had ever recorded, with an amplitude and duration that were *eight times greater* than those we usually recorded in normal light-adapted conditions (Sheliga, Chen, FitzGibbon, and Miles, 2006). Perhaps the rod-driven OFR is not subject to divisive normalization? Under these scotopic conditions, reversal of the OFR occurred only with longer ISIs and was very weak, reasonably consistent with the human psychophysics.

The Torsional Ocular Following Response

On a whim, I decided to see if a motion stimulus that rotated the retinal image around the line of sight ("circular optic flow") would elicit torsional

eye tracking at short latency, even though it involved a motion that would normally be associated with *rotational* disturbances of the observer (in contrast with all of our other motion stimuli, which would normally be associated with *translational* disturbances of the observer). For this, we replaced our usual search coils with the ingenious figure-eight search coils that Han Collewijn's laboratory had designed especially for recording torsional eye rotations (Collewijn, Van der Steen, Ferman, and Jansen, 1985), and we redesigned all of our visual stimuli so that the subject now always saw images rotating around the lines of sight, that is, circling around the fovea (Sheliga, FitzGibbon, and Miles, 2009). An initial experiment using random-dot patterns soon revealed that, indeed, there were robust torsional responses, though with latencies approximately 15 ms longer than for the usual OFR.

With 3*f*5*f* circular gratings arranged like the spokes of a wheel (see Figure 2C) as well as 3*f*7*f* circular gratings, the torsional eye movements elicited by quarter-wavelength steps of angular rotation showed a clear dependence on the motion of the two Fourier components rather than on the motion of the overall features, again consistent with mediation by spatio-temporal filters sensitive to motion energy, and showed a highly nonlinear dependence on the relative contrast of the two gratings that resulted in WTA behavior when their contrasts differed by more than an octave. Thus, the neural mechanisms sensing the two overlapping rotational motions were negatively cross-coupled as though subject to mutual inhibition, regardless of whether those motions were in the same or in the opposite direction. When the 3*f* and the 5*f* circular gratings were each reduced to a single annulus of the same radial thickness (3°), WTA behavior was evident only when the two overlapped (same radius) and not when they were separated (different radius), that is, the nonlinear interactions were local. These various stimulus dependencies were, in all essentials, like those we had previously seen with the horizontal and vertical OFR and could even be described by the same mathematical functions, often with very similar parameter values. Accordingly, we referred to these initial torsional eye movements as the tOFR. However, there was one major surprise: The tOFR showed much weaker spatial normalization than the horizontal OFR, and Boris Sheliga discovered that this had a very interesting consequence. Using a circular grating consisting of a one-dimensional sinusoid partitioned into a number of equally spaced concentric annuli all of the same radial width (that could be 0.5°, 1°, or 1.5°) and same contrast (that could range from 2 percent to 32 percent), Boris found that the latency and the magnitude of the tOFR were well described by single monotonic functions if plotted against the product of the total area of the annuli and the square of their Michelson contrast ($A*C^2$). It was as though the onset and magnitude of the tOFR were determined simply by the *total motion energy* in the stimulus! Boris also reanalyzed our old horizontal and vertical OFR data and found that,

when plotted against $A*C^2$, a single monotonic function sufficed to describe the latency but not the magnitude. The latter was inevitable, given that the OFR was subject to such powerful spatial normalization whereby responses failed to grow with fivefold increases in stimulus area. Thus, the global organization of the tOFR provided some new insights into the distribution of the mutual inhibition thought to underlie the divisive normalization of the OFR: these inhibitory connections extend horizontally and vertically, but not circularly around the fovea.

The Disparity Vergence Response: Independent Sensing of First- and Second-Order Disparity

Based on the initial DVRs recorded when disparities were applied to anticorrelated random-dot patterns, *mf* stimuli, and 3*f*5*f* stimuli, we had concluded that the earliest vergence was a response to the disparity energy in the stimulus. However, there is substantial evidence for stereopsis when disparity is applied to binocular stimuli that lack first-order energy because they are defined not by luminance but by a second-order characteristic such as contrast. In what was to be my last project, Holger Rambold (a postdoctoral fellow from Germany), Boris Sheliga, and I recorded the initial DVRs elicited by disparity stimuli in the form of one-dimensional sinusoidal gratings with a binocular phase difference of one-quarter-wavelength, created by luminance modulation (LM) and/or contrast modulation (CM) of a dynamic noise carrier that was uncorrelated at the two eyes (see Figure 3A–C). We showed that gratings defined by CM at both eyes (Figure 3E) elicited robust DVRs that worked to reduce the quarter-wavelength disparity (i.e., gave greatest weight to the nearest neighbor matches). One problem here that had to be taken care of was that compressive nonlinearities early in the visual pathway were known to result in first-order distortion products that can render even pure second-order stimuli—such as the CM stimuli—visible to first-order (energy-based) detectors. However, we were able to show that disparity stimuli defined by CM at both eyes still elicited robust DVRs—although at slightly longer latency ($\sim$ 20 ms)—even after such early first-order distortion products had been nulled by adding in-phase LM at both eyes, consistent with mediation by cortical mechanisms selectively sensitive to disparities defined by the second-order CM. Hybrid first- and second-order disparity stimuli—in which one eye saw a grating defined by LM and the other saw a grating defined by CM with a binocular phase difference of one-quarter-wavelength (Figure 3F)—generated only weak DVRs that were always in the "wrong" direction and had the ultra-short latencies associated with first-order DVRs, consistent with mediation by first-order distortion products associated with the CM stimulus. In fact, these (reversed) DVRs could be eliminated entirely by adding a small amount of in-phase LM to the CM stimulus that was exactly equivalent in magnitude to the first-order

distortion products seen earlier. Various controls indicated that the failure of the hybrid LM and CM stimulus to elicit DVRs after nulling any first-order distortion products was also not due to differences in the amplitude, spatial

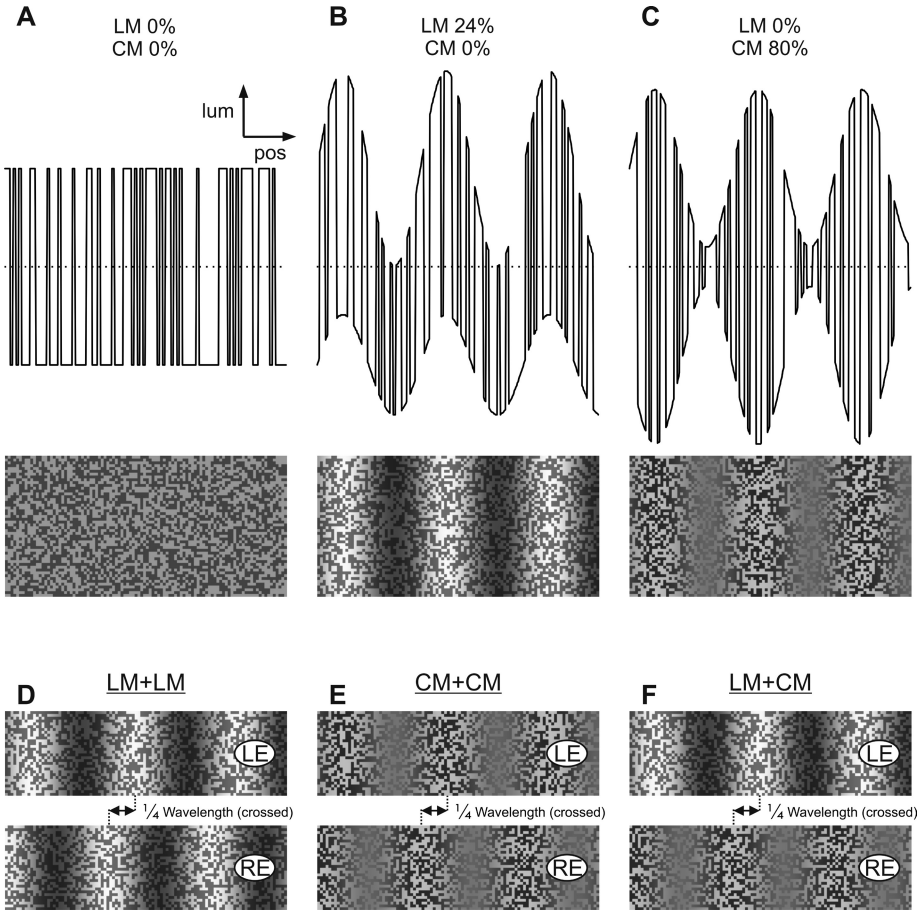

Fig. 3. Sample disparity stimuli. (A–C) One-dimensional sinusoidal gratings created from a dynamic binary noise pattern (A), by luminance modulation (B), and contrast modulation (C); the upper plots show sample cross-sections of the luminance and the lower panels show the patterns as seen by the observer. (D–F) Patterns as seen by the observer when disparity stimuli in the form of one-dimensional sinusoidal gratings with a quarter-wavelength binocular phase difference were created by luminance modulation at the two eyes (D), contrast modulation at the two eyes (E), and luminance modulation at one eye and contrast modulation at the other eye (F). (LE, left eye. RE, right eye.) Such beautiful patterns would not be out of place in an art gallery. From Rambold, H.A., Sheliga, B.M., and Miles, F.A. (2010). Evidence from vergence eye movements that disparities defined by luminance and contrast are sensed by independent mechanisms. *Journal of Vision, 10*(14): 31, 1–34. With permission.

phase or timing of the inputs from the two eyes, leading to the conclusion that the cortical detectors sensing disparities defined by first-order LM and second-order CM must be independent. These findings were published in my last paper (Rambold, Sheliga, and Miles, 2010). Of course, the methodology in this study could also be used to look for OFRs and RFVRs to second-order stimuli defined by contrast.

Epilogue

The emphasis in this memoir has been on my research—mostly what I did and how I came to do it—with little about my private life except during the early years before I entered science. Some will find it too detailed, but it seemed the only way to capture the full flavor. Always one hoped that the ideas would be novel, the methodology would be rigorous—perhaps even elegant—and the data would be decisive. Of course, things often fell short of that, and looking back, I think the last phase of my research perhaps came closest, when the turnover of ideas was satisfyingly rapid and everything was completely quantitative. During this period, I found it especially pleasing that, almost always, stimulus dependencies could be modeled with simple mathematical expressions that had only one or two free parameters and yet described at least 95 percent (often, 99 percent) of the stimulus-induced variance. This is so rare in neuroscience. It was also deeply satisfying that many of the local spatiotemporal characteristics were so like those of neurons in the monkey's striate cortex; it was as though we were probing the neural processing in the human striate cortex, even though we were actually recording only *motor* responses. Almost by chance, we had happened upon a beautiful way to study the human visual system. Perhaps an important factor here was that, at any given moment, there could be only one eye movement, and our reflex responses were the culmination of a prodigious amount of neural processing that represented the nervous system's best initial estimate of what was in the subject's best interests. I thought that alone made them deserving of close study.

I retired in 2010 after almost 40 years at the NIH. I had had the ideal situation—a well-equipped laboratory, a steady stream of talented and highly motivated coworkers, no teaching, and minimal administrative duties. It was rare for me to have more than one or two postdoctoral fellows at a time, allowing me to spend most days working with them in the lab rather than administering a group from an office. I always felt that close contact with the raw data was imperative if the many potential pitfalls in research were to be avoided. Even so, constant vigilance—and numerous controls—were always needed if one wanted to lay claim to a genuine advance. In my last year or so in the lab, I began to notice that I could not always recall the details of a given experiment and would have to check with my colleague: I was no longer a reliable source of information, and retirement was the

only option. But I was well satisfied. I had had a good run, and it was time to turn to other things: family, friends, reading, travel, opera, concerts, art exhibitions, theatre, the outdoors, and so on and so forth.

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