Emilio Bizzi

Born:

Rome, Italy
February 22, 1933

Education:

University of Rome, Rome Italy, M.D. (1958)
University of Pisa, Pisa, Italy, Docenza (Ph.D.) (1968)

Appointments:

MIT, Eugene McDermott Professor in the Brain Sciences and Human Behavior (1980–1983)
MIT, Director, Whitaker College of Health Sciences, Technology, & Management (1983–1989)
MIT, Chairman, Department of Brain and Cognitive Sciences (1986–1997)
MIT, Eugene McDermott Professor in the Brain Sciences and Human Behavior (1997–2002)
MIT, Institute Professor (2002–)

Honors and Awards:

Medical degree with highest honors (summa cum laude) (1958)
Alden Spencer Award (1978)
Hermann von Helmholtz Award (1992)
Secretary of The American Academy of Arts and Sciences (1999)
Italian National Academy (Accademia dei Lincei-Rome) (1998)
American Academy of Arts and Sciences (1980)
National Academy of Sciences (1986)
Degree "honoris causa" in Biomedical Engineering, University of Genova, Italy (2004)
Empedocles Prize (2005)
Institute of Medicine of the National Academies (2005)
President of Italy Gold Medal for achievements in science (2005)
President, the American Academy of Arts and Sciences (2006)

Early in his scientific career, Emilio Bizzi studied the neurophysiological mechanism of sleep and discovered a functional connection between an area of the brain stem and the visual areas of the brain. Later on, his research focused on the physiological mechanisms underlying complex, coordinated movements. His results have formed the basis of a comprehensive theory—the equilibrium-point hypothesis—which accounts for how the central nervous system solves the complex computational problem of executing limb movements. Recently, his laboratory has provided evidence that internal representations of limb dynamics are built by combining modular primitives found in the spinal cord as well as other building blocks in higher brain structures. He has also investigated motor learning and the problem of consolidation of motor memories.

Emilio Bizzi

In the 1950s when I enrolled in Rome's medical school the word *neuroscience* did not exist. Scant instructions on the brain's anatomy and physiology were of course imparted as part of teaching of human physiology, but greater prominence was accorded to the heart, the kidney, and especially the digestive apparatus. No wonder that in my somewhat anxious and idle speculations about my professional future the idea that that I would have ended up as a neuroscientist never occurred to me.

While "neuroscience" was not part of my horizon, it very soon became clear to me that I had a sharp interest for the scientific underpinnings of medicine—I did not know what kind of research I wanted to do—I simply had a yearning for a life devoted to biological investigations rather than the practice of medicine. It is now obvious to me that my early inclinations toward a research career derived to some extent from my family environment. My maternal grandfather, an outstanding surgeon in Milan, was highly regarded in the family more for his contributions to innovative methods in medicine than for his remarkable surgical skills. Another close relative, an uncle, who became Professor of Gynecology at the University of Parma, was known for his investigations of the biological mechanisms of reproduction. But the person that I found most impressive was my grandmother's brother. A well-known botanist, an enthusiastic, passionate man, totally committed to his research, a member of the Italian National Academy (Accademia dei Lincei, who had had Galileo among its members), he used to visit us when he travelled to Rome to attend the Academy's sessions. His engaging, passionate descriptions of his searches for exotic plants and flowers in the most remote corners of the Italian mountains are still on my mind as an example of a happy, fulfilling life in the pursuit of knowledge.

In addition to my family environment, my professional future was shaped by the sociopolitical environment that was prevalent in post–world war Italy. Science and intellectual pursuits were highly regarded values, at least in the social circles to which I belonged. After the years of a repressive regime and a devastating war, Rome in the 1950s was a city eager to catch up with modernity; its citizens, deeply involved in political-ideological controversies, generated an environment foreign and perhaps even unfriendly to middle-class, bourgeois values. I was excited to be centered in this uniqueness and was like a sponge absorbing all of these novelties that represented to me a totally different experience from the rigid, somewhat puritanical background of my parents.

Inevitably, as prosperity slowly took roots and as a consumer-oriented environment became prevalent in Italy, that special postwar atmosphere changed. I often still think of those years with a nostalgic feeling, and I am fond of reminiscing about specific events and people I met, but, most of all, I recognize the powerful formative role of those years.

On balance, at medical school I had 6 happy years. In the first 2 years I acquired a decent background in the basic sciences such as chemistry organic and inorganic, physics, lots and lots of human anatomy, and biology. The last 4 years were more fun; I learned about pathology, human physiology, and the clinical specialties. Because students were not compelled to attend the lectures, I had time on my hands that I utilized by working as an intern in the Department of Pathology. I choose pathology because this discipline's approach allowed a mechanistic understanding of the devastations induced in the body's organs by disease. In addition, the Department had an outstanding reputation. All of this made sense to me, and I still remember how happy I was when the Chair of Pathology told me that I had won the highly competitive privilege of becoming an intern. What I had not taken into account was that the "privilege" really entailed an out-of-the-ordinary daily routine that I was obliged to follow.

My duties, I was told, were relatively simple: while the pathologist went on with his business of dissecting a cadaver by extracting and then examining one by one all of the deceased's organs, I was to write down the pathologist's comments and findings. And, this was in addition to doing my own job every morning—five days a week! The first weeks were really tough—the revolting stench and the gruesome, horrific sights of the procedures were hard to take. But, surprisingly, in the course of a month or two I became used to this unusual universe and began gradually to take an interest in the erudite medical discussions among the pathologists and the physicians that had treated the diseased. Discussions that, incidentally, took place right there in that foul-smelling room.

In retrospect, I still wonder what compelled me to begin my days in this definitely out-of-the-ordinary way. Granted I learned a great deal about medicine, but at what price?

As an intern my duties were not limited to taking notes but included work toward an experimental thesis. My task was to collect tissues from patients that in spite of robust treatment with antimitotic drugs had died of leukemia. This was my "research" assignment, and I dutifully collected all the samples I could in the 2½ years of my internship. I then prepared the samples for histological examination, and in the process I learned much about classical staining technique and how to be familiar with the cellular patterns of different organs. In the end, my diligent efforts were rewarded with a cum laude degree.

I must confess that as I proceeded with my thesis I felt an intense boredom for the type of work I was doing—if this type of descriptive work passes

for "research" I was not going to select a career in science. Part of my discomfort was the oppressive intellectual narrowness of the scientific environment of the Pathology Department, which in a sense prevented me from acquiring a broader view of science. The faculty consisted of very serious, hard-working, quasi-monastic investigators whose sense of moral superiority left me cold. The Department was a very inward-looking place; scientists from the outside world would rarely visit, and I do not recall having ever attended a seminar in my 2½-year tenure there. Quite a contrast with today's departments where the opposite is the norm, and we are constantly flooded by a stream of talks presented by scientists frenetically on the move from place to place.

Clearly research in pathology was not what I was going to consider, but the dislike for the type of descriptive science to which I had been exposed made me question the idea of a career in science. Not surprisingly, the day after my degree was awarded, I felt uncomfortably directionless.

If a career in the unappealing science to which I had been exposed during my student years looked doomed, maybe work in medicine was worth exploring. I therefore applied to the university hospital in Siena and became a member of the staff of the Internal Medicine Department. Siena, an attractive small medieval city about 50 miles south of Florence, had a good medical school, a good teaching program, and, surprisingly for a small provincial, out-of-the-way university, an excellent research program focused on the physiology of the hypothalamus and the reticular formation of the brain stem. I was fortunate in that the leader of the group, Alberto Zanchetti, needed an assistant and asked me to join his research team. From that time forward my days were divided by clinical duties and research.

The combination of clinical service and laboratory work meant long hours, 7 days a week. But in spite of the heavy time commitment, and the almost total disappearance of my social life, I had 2 happy years in Siena. I found medicine and research to be exciting. To be at the bedside collecting the clinical history of a newly admitted patient, to perform the physical examination, and then attempt a diagnosis was an exciting and entirely novel experience. I quickly realized that the body of medical knowledge I had acquired during my pathology days was immensely useful for the understanding of medical riddles and in formulating a diagnosis. The training in pathology I had acquired through the observation of countless autopsies gave me a systemic view of medicine. For instance, when confronted with patients whose liver had been affected by years of heavy Chianti drinking (Siena is at the heart of the Chianti region), I could not only visualize the macroscopic aspects of the diseased liver and the altered cellular configurations, but could also understand its systemic consequences on other organs and the panoply of symptoms could be logically deduced.

Research turned out to be equally exiting. I began as a lowly assistant in charge of cleaning up the surgical instruments and the mess after small

animal surgery. However, I did not mind the drudgery of these tasks because I felt privileged to be able to observe, for the first time, "real" scientific work deployed before my eyes. At that time, the late 1950s, some of the leading neuroscientists were investigating the functional properties of the reticular formation. The seminal paper that sparked a great deal of research on this topic had been published in 1949 by Moruzzi and Magoun. This paper, which resulted from a collaboration between Horace Magoun, a neuroanatomist at the University of Chicago and a visiting professor from Pisa, Giuseppe Moruzzi, showed that electrical impulses delivered to the reticular formation (RF) could change the cortical electroencephalogram (EEG) from a pattern characterized by slow waves (like in sleep) to a desynchronized, high-frequency pattern similar to the one present during waking, arousal, and attention. Incidentally, the reticular formation is an anatomical structure located in the pons and the mesencephalon made up of groups of highly interconnected interneurons, of cells receiving input from spinal cord, from cortical and subcortical areas, and from the cerebellum. In addition these are the cells of origin of long fibers projecting to a number of subcortical areas. The anatomy is very complex, but at that time the reticular formation was conceived to be a functional entity capable of regulating the sleep/wake cycle as well as other behaviors.

The project in which I became involved was aimed at understanding some aspect of the reflex regulation of the reticular formation. The model system involved removing all the central nervous system (CNS) structures rostral to the posterior hypothalamus in the cat. The resulting preparation, when appropriately stimulated, displayed the behavior of "sham rage,"—the behavioral sign that activation of the reticular formation and the rostral hypothalamus had occurred. The goal of the research was to explore whether a sham rage attack could be evoked by manipulating the level of blood pressure in a reflex way. We tested the hypothesis that the receptors from the carotid body were conveying impulses that exerted an inhibitory influence to the rostral part of the reticular formation and posterior hypothalamus. We found that by lowering abruptly the blood pressure, thus eliminating the steady flow of impulses originating in the carotid body receptors, an attack of sham rage could result.

I must admit that I found these experiments fascinating—controlling behavior, albeit a highly bizarre behavior like sham rage, through a simple reflex manipulation and localizing to a specific neural structure a highly complex and integrated behavioral response meant getting in touch with a dynamic world of doing science that contrasted with the static experience I had with pathology. What fascinated me and ultimately hooked me to the field of neuroscience was the possibility of studying in a mechanistic way the neural underpinnings of important brain functions.

To me the exposure to experimental science in Siena was similar to the sudden love for classical music that happened when I first heard Beethoven's

symphonies. I went from a person indifferent to classical music to a passionate pursuit of more and more classical music. Needless to say that as I began work in Siena in the late 1950s, I was actually entering the field of neuroscience with no idea of its future developments. But the limited exposure to neurophysiological research experienced in Siena was so compelling that I decided to leave the medical department and a career in academic medicine to get full-time training in neurophysiology. At that time the best place for brain science in Italy was at the University of Pisa in the institute directed by the famous Giuseppe Moruzzi.

The Years in Pisa

In 1960 when I began my training at the Institute of Human Physiology of the University of Pisa, Giuseppe Moruzzi was the uncontested, the highly respected leader, and the absolute ruler of the department. He was a deeply serious person, physically imposing, with a passion for scientific ideas, courteous, but distant and somewhat intimidating; a person totally committed to research who I came to admire, but perhaps not love. At that time, Moruzzi was pursuing a number of lines of research all connected to his main interest: the functional properties of the reticular formation.

In the early 1960s research was poorly funded in Italy, but the Institute in Pisa was a lucky island because Moruzzi had been able to set up a fairly large department, where six to seven groups could conduct investigations with fairly up-to-date equipment. Incidentally, some of the funds came from the U.S. Air Force program, which provided badly needed support in the postwar years. Another feature of the department was the presence of a significant contingent of foreign investigators. As a rule each Italian investigator was teamed with a foreign fellow. To each team he assigned a research theme, he told what experimental approach we were expected to follow and what outcome he expected. He was perfectly comfortable with discussing the details of the investigations, the strategic approach, but he made it clear that the team was going to purse the research topic that he proposed. Naturally, this top-down display of authority did not sit well with some of the more mature foreign visitors; for me, there was no problem. I was a beginner, and it would have been impossible for me to put forward a research plan of my own.

During my first year I was lucky. I was teamed with Alden Spencer, a talented young investigator from Portland, Oregon, who had worked at the National Institutes of Health (NIH) where he had learned the technique of intracellular recording while investigating the properties of the hippocampal cells in collaboration with Eric Kandel. I learned a lot from Alden. He liked to talk about his U.S. neuroscience experience; the people he met at the NIH, the various areas of research he thought were promising and exciting. His stage at the institute was, however, almost a total failure. He did not like the research theme assigned to us, we did not accomplish anything

scientifically relevant, and Alden ended up the year quite unhappy. Although I understood and sympathized with Alden's disappointment, I was not too unhappy; I had learned a lot even from the failed research experience, but especially from Alden.

During my second year my foreign collaborator was Dana Brooks, a neuroanatomist from Cornell Medical School. Moruzzi told us to investigate the origin of the slow potentials that appeared in certain areas of the pontine reticular formation during rapid eye movement (REM) sleep. These slow potentials had been described by Michel Jouvet, a French investigator who was one of the major forces behind research on the neural mechanisms underlying the different phases of sleep. Dana, who had visited Ed Evarts laboratory before coming to Pisa, brought with him a copy of the Evarts microdrive. This microdrive allowed us to position recording electrodes in almost any corner of the cat's brain. With this device, which we connected to the skull of the animal, we were able to map the pontine slow potentials during the REM phase of sleep. The mapping experiment lasted a few tedious months, and after a while it became gradually clear to us that we would not be able to draw interesting functional conclusions by this exercise. We would have produced a map of electrical events during sleep, but the "so what" thought began creeping in our daily conversations. Before discouragement really set in, something unexpected occurred. At that time I had the habit of reading everything that was published on sleep, and I happened to read a small abstract describing the presence of strange slow potentials in the lateral geniculate of the cat during sleep. I spoke to Dana, and immediately we implanted electrodes in the pontine reticular formation (in the areas we had mapped) and the lateral geniculate. We were thrilled when during the first episode of REM we observed the almost synchronous appearance of slow potentials in the pons and the geniculate. That meant that an extraretinal input was reaching a structure devoted to the transmission of retinal impulses to the visual cortex. In the months following this observation we figured out that the pons was the site of origin of the slow potentials and that the potentials were transmitted from the geniculate to the visual cortex. These ponto-geniculate occipito (PGO) potentials became well known because they were related by others to the visual imagery of dreams.

Before Dana departed for Cornell we wrote a paper that was published in *Science*. I have often reflected on the serendipitous and lucky circumstances that led us from a tedious, undistinguished mapping experiment to an exciting finding. Later on I had similar experiences where luck, not skills or deep insights, changed the course and the relevance of my research.

During the third and final year of my stage at the Institute in Pisa, my collaborators were Professor Ottavio Pompeiano and a Hungarian postdoctoral fellow, I. Somogyi. We again worked on REM sleep but focused on the pattern of discharge of the cells of the vestibular nuclei. In particular we wanted to record from the cells of origin of the lateral vestibular nucleus. From these

cells originate the descending vestibulo-spinal tract, which makes monosynaptic connections with spinal motoneurons. This pathway plays a major role in the control of vertebrate posture. During REM sleep there is complete disappearance of muscular activity especially in postural muscles. Hence, it made sense to ascertain the role of the vestibulo-spinal pathway. Technically, these were not easy experiments, but somehow we managed to record from the vestibular nuclei during REM and found that the cells of the lateral vestibular nucleus did not change their firing rate during the disappearance of the muscular activity in postural muscles. This was clearly a counterintuitive result that suggested the existence of an inhibitory activity conveyed by other descending tracts; a suggestion that was later pursued successfully by Pompeiano. We described the cells we had recorded from the four main vestibular nuclei and published a short paper in *Science*.

At this point I was ready to move to another environment and begin to be independent. Although the research on sleep had been satisfactory, I was not sure that I wanted to pursue that line of investigation. I was quite certain that I would not have been able to understand the origin and the function of sleep with the electrophysiological techniques I had learned. Certainly, I could have continued to accomplish a number of descriptive studies in the area of sleep, but I felt as if that was like nibbling at the problem on the periphery.

St. Louis, Missouri

The opportunity to have a laboratory of my own and investigate problems of interest to me presented itself quite unexpectedly when I met Rita Levi-Montalcini in Rome. She had recently discovered the nerve growth factor, a discovery that made her famous and earned her the Nobel Prize. When I met her she had an active laboratory at Washington University that included a fully equipped neurophysiology set up. She needed somebody to run it, and when she offered me the position of research associate, a laboratory with technical assistant and start-up funds to carry on my research, I instantly and happily accepted her offer. The prospect to visit and work in the United States and to get to know and interact with the vast U.S. research community was very appealing and played a role in my decision to leave the Italian academic community. By the middle of July 1963, I was in St. Louis, Missouri, getting acquainted with the new world.

St. Louis had been an important center for brain science. Erlanger and Gasser, who had earned the Nobel Prize for neural transmission were emeriti professors, but still active members of the community, and so were O'Leary and Bishop. On the main campus, the neuroembryologist Victor Hamburger was an intellectual force and, naturally, Rita Levi-Montalcini with whom I established a lasting friendship, was the star of Washington University. The

importance of the nerve growth factor was already widely recognized, and there were many demands on her time from all the corners of the world. I did not join her group but pursued a theme that was related to my previous work on PGO waves. I wanted to establish that the visual pathways, at the level of the cells of the lateral geniculate, received an extraretinal input during the slow potentials of REM. Not surprisingly, I found that the geniculate cells were activated when the animal in complete darkness went though the REM phase of sleep. I quickly described these findings in a paper for the *Journal of Neurophysiology*. This paper has the unique distinction to be the only paper I ever had accepted without any revision.

Toward the end of my year in St.Louis, I considered yet another move to a larger and more active scientific community. I also felt that I needed additional training. After visiting various east coast laboratories I opted for a stage at the NIH with Ed Evarts.

The Years at the NIH

There is no question in my mind that Ed Evarts, the Director of the section on motor control of the National Institute of Mental Health, was an outstanding scientist. His approach to the study of the way in which the CNS generates voluntary movements has had a lasting influence on the field of motor control. His style of research and the methods that he invented have been adopted by large number of investigators in the United States and abroad. But if Ed Evarts the scientist was unquestionably admirable, the man was something else: difficult, cold, and to a certain extent, mean spirited. To this day, when Tom Thach, Peter Strick, Mahlon DeLong (all of them have been postdoctoral fellows in Ed's lab), and I get together at meetings, we rehash memories of humiliation and fears.

When I entered Ed's lab in the summer of 1964, I had a simple plan; I wanted to learn his methods and his approach to motor control. After all, this is why I had left first Pisa and then St. Louis. I needed to find new research avenues because sleep research was no longer my choice. At our first meeting, I naively told him, "I am here to work with you"; Ed's facial expression left no doubt in my mind that I had made a gigantic faux pas. After a long silent moment, and without answering my question, he told me that I was going to be on my own and that I should tell him what kind of project I wanted to do. After a somewhat painful discussion—many of the projects I was mentioning were scornfully rejected—he agreed that I could explore the idea that the REM slow potentials in the lateral geniculate could represent massive presynaptic depolarization of the optic tract terminals. He expressed skepticism about the viability of my project but reluctantly gave me his O.K. Although this was not the outcome I had hoped for, I was not unhappy with the presynaptic project; it was, after all, my idea and presynaptic inhibition

was a hot topic at that time. In addition, there were no experiments showing that presynaptic inhibition was working in vivo in a behavioral context.

I started experimentation immediately in the miniscule, underground cubicle I was going to occupy for the next 2 years. For the first 3 to 4 months I had no results, and as time went by, I was spending more and more frantic hours in the cubicle but to no avail. Each time I emerged from underground I was aware of Ed's glare, indicating that my reputation was crumbling. Finally, the dreaded moment came; Ed told me that I should end the unproductive project right away. I pleaded for more time and, surprisingly, he agreed: "One more month and that's it," he said.

My pleading was not a desperate attempt at prolonging what so far had been a failure but was based on my reading a recent paper that described a novel way to test for presynaptic inhibition. After the dreadful conversation with Ed, I implemented the new approach and got clear evidence for depolarization of optic tract terminals during the slow potentials of REM sleep. This observation was important because it decreases the retinal influence on the visual pathways during REM sleep while the neural signals from the pons reach the visual cortex via the lateral geniculate body.

In the following days I repeated the experiments a number of times, and when I finally became convinced that the result was real, I asked to see Ed. His response left me deeply disappointed and angry—he simply did not believe the results. He asked for a series of controls and without additional words ended our meeting. In the following days I started to look around the Washington area for another laboratory. Then something totally unexpected happened. One morning I arrived in the laboratory late and to my great surprise I noticed a smiling and welcoming Ed waiting for me. He told me that he had just read that Japanese investigators had achieved results essentially similar to mine. In a normal environment such an event would be considered almost a disaster—being scooped is one of the fears of scientists. In this case I jumped for joy because not only had I gotten external confirmation of my results, but this event transformed Ed's attitude toward me. From that time on I was a kind of hero, I could do no wrong, and my opinions were considered with interest and respect. To understand what Ed's volte-face meant to me, one should consider that the position of postdoctoral fellow is very precarious. Lack of support from the head of the laboratory may spell doom for the fellow's career, and a foreign postdoctoral fellow is even more vulnerable.

After the completion of the presynaptic work, I was finally allowed to utilize Ed's technique of single neuronal recording in behaving monkeys. I recorded from the cortical motor area controlling the eyes—the so-called frontal eye field that is located in the frontal lobe along the arcuate sulcus. Technically this experiment turned out to be easy, and in a short amount of time I was able to provide, for the first time, a description of the pattern of discharge of cortical cells during saccadic and smooth pursuit eye movements.

Recording from the frontal eye fields revealed a number of unexpected results. Unlike the cells of the classical motor cortex (area 4), most of the eye-related cells discharged during or after the saccades. Only a few seemed to be active prior to an eye moment. These observations suggested different functional properties between these two motor areas.

The recordings from the frontal eye field ended during the summer of 1966. At that point I was ready to be on my own. During the years in Pisa, St. Louis, and Bethesda I had gained technical knowledge with instrumentation and the surgical skill necessary to conduct animal experimentation. I also had a clear idea of what I wanted to do in neuroscience. My problem was to find a suitable environment to pursue an academic career. It was also clear to me that I wanted to be at a university rather than a scientist in a government laboratory such as the NIH.

The opportunity to obtain a university position arose when I met Hans Lukas Teuber. Teuber, an outstanding neuropsychologist who had been appointed in 1964 as chair of the MIT Department of Psychology, was known for the excellent appointments he had made. The faculty he had hired reflected his goal to establish a neuroscience group rather than a traditional psychology department. Because behavioral neurophysiology was going to be the central core of his department, Teuber was keen on importing the recording techniques Evarts had developed. And when he asked Evarts if he knew of anybody willing to move to Boston, Evarts mentioned my availability and I got an offer that I could not refuse.

The Years at MIT

I was thrilled to be at MIT. The department was a lively place; in addition to Teuber, the leading investigators were Walle Nauta, Richard Held, and Jerry Fodor. But brain science was also well represented in other departments and centers. For instance, in biology Jerry Lettvin, Pat Wall, and W. McCulloch were extraordinary scientists, colorful, irreverent personalities, always ready to engage in vigorous discussions and great fun to be with.

Motor Coordination

During my first year, in collaboration with Peter Schiller, we recorded from the monkeys' frontal eye field neurons during the coordinated movements of eyes and head. In the following years I became more and more interested in the way in which the CNS succeeds in coordinating the movements of different body parts.

I thought that the coordination between the eyes and the head was a good way to begin. The head, a big mass relative to the eyes, is controlled by a large number of muscles and moves with a relatively slow velocity compared with that of the eyes.

Eye–Head Coordination

In foveate and unfoveate species, the most common response to target presentation is the coactivation of eye and head muscles. To direct the eyes and head toward a target and then fixate it with the fovea, an animal must solve three problems. First, it must compute the angular distance between its foveal lines of sight and the target. The absolute magnitude of this distance, called "retinal error," will determine to a first approximation the amplitude of the saccadic eye movement that will be produced. Second, the animal must initiate a head movement that will be compatible in amplitude with the saccadic eye movement. Third, because the eyes usually move first and with higher velocity than the head, their lines of sight will reach and fixate the target while the head is still moving; to maintain fixation on the target, the animal must make a rotational eye movement counter and proportional to the movement of the head. This maneuver, which keeps the fovea constantly on the target, is called a "compensatory eye movement." I will consider these problems separately.

Saccades During Head Movement

Because the head may begin to move before, at the same time, or a few seconds after the eyes move, saccades often take place while the head is moving. The data we collected indicated that the animal fixated the target with the same precision with and without head movement. However, the saccadic eye movements during unrestricted head movements were decreased in amplitude, duration, and peak velocity.

This finding that I published in *Science* in 1971 (in collaboration with R. Kalil and V. Tagliasco) raised the question whether the decrease in saccade amplitude, duration, and peak velocity during head turning was the result of an adjustment of the central oculomotor program caused by head movement. We found that the central mechanisms responsible for programming saccades takes account only of target position and that no information is transmitted from a head programming mechanism to the oculomotor system. Hence, the decrease in saccade amplitude, duration, and peak velocity must be mediated by reflex activity originating from structures excited by head turning: the vestibular apparatus and neck proprioceptors.

In the monkey, vestibular afferent signals are responsible for modulating saccadic eye movement. I demonstrated the crucial role of these signals by surgically interrupting the pathway linking the vestibular receptors to the vestibular nuclei. For several weeks after the operation (before the monkey had learned to compensate for the loss of vestibular input), saccades made with and without head movement were identical in amplitude. During head turning, the unmodulated eye movement was simply added to the head movement and the gaze overshot the target (work in collaboration with J. Dichgans).

The reflex mechanism is clearly more advantageous to the animal than a central mechanism for modifying saccades. Because the vestibular system automatically nullifies any displacement of the fovea from the target as a result of head movement, the motor programming systems responsible for eye–head coordination can program eye and head movements independently. Because the vestibular reflexes monitor the actual movement of the head, they can adjust saccadic eye movements to compensate for any unpredicted peripheral load or resistance that changes the course of a centrally initiated, intentional head movement.

Compensatory Eye Movements

The modification of saccades is only one aspect of the interaction between central oculomotor programming and reflex activities generated by head turning. Although this interaction plays a decisive part in the process of target acquisition, feedback from peripheral sensory organs also plays a role in the control and generation of compensatory eye movements. These movements by being counter to head motion, but of equal amplitude and velocity, keep the eyes on the target during head turning. Such movements have been observed in every species that has moving eyes. Compensatory eye movements are critically influenced by input from vestibular, and only minor effects derive from visual receptors and neck proprioceptors.

Head Movement

In collaboration with Morasso and Tagliasco, I showed that the events that follow the sudden and unexpected appearance of a target in the visual field occur in the following order: the saccadic eye movement begins first, and then, after 20 to 30 milliseconds, the head begins to move in the same direction. The electromyographic (EMG) records show, however, that the eye muscles begin to contract 20 milliseconds after the neck muscles are activated. The overt sequence of eye and head movements thus does not reflect the order of neural commands.

Simultaneous recordings from several neck muscles during horizontal head rotation have shown that all of the neck agonists are activated synchronously. Concurrently activity is suppressed in all of the antagonists. The agonist muscles are synchronously activated regardless of initial head position; however, the amplitude and duration of initial bursts of neck muscle activity are related to the starting position and amplitude of the head movement.

In the simple case in which the monkey's eyes are centered in the orbit and triggered head movement begins from the straight-ahead position, there is a consistent relationship between the magnitude of the target displacement and the amplitude and velocity of the head movement. This relationship is

qualitatively very much like that between target displacement and saccadic movements of the eyes.

In general there is no fixed relation between retinal error and the amplitude of the head response. Thus for head movements to be coordinated with eye movements, the system controlling head movement must have constant access to information about the position of the eyes in their orbits. This information could be supplied by eye proprioceptors or by oculomotor collaterals. Indeed eye muscle afference has already been described. Furthermore there is evidence suggesting that the position of the eyes in their orbits is coded by corticofugal neurons in the frontal eye fields, and a population of brain stem cells that encode eye position has been found.

Schematic Outline of Eye–Head Coordination

In the very simple case in which a single target light is flashed in the visual field of a monkey looking straight ahead, the eye–head sequence begins with the detection of the target. Motor programs involving the head and eyes are activated and send impulses to eye and neck muscles. These impulses produce saccadic eye movement and a head movement that activates vestibular receptors. Signals from these receptors modify saccadic duration and velocity and generate a compensatory eye movement that allows the fovea to remain fixed in relation to a point in visual space during head rotation. The fixation permits a second visual sampling, then a third, and so on, with opportunities for correcting errors at each sampling. This closed-loop scheme makes it clear that the role of the central motor program in eye–head coordination is simply to initiate eye and head movements. Because there is no central programming of saccadic adjustment or compensatory eye movement, the functional, or behavioral, coordination of head and eye movements depends on the modification of centrally initiated movements by signals triggered by receptors in the vestibule of the inner ear. This conclusion simplifies our view of the neural mechanism underlying motor coordination insofar as, contrary to common assumptions, there is no need to postulate a special population of "executive" neurons with exclusive responsibility for coordinating eye and head movements. Coordination is an emergent property of the CNS.

Eye–Head Coordination During Smooth Pursuit

Human beings, monkeys, and cats use a combination of eye and head movements to track a moving visual stimulus. These two kinds of movements are coordinated through the integration of centrally generated commands to the motor systems of the eye and the head with afferent activity originating from visual and vestibular receptors and neck proprioceptors. In experiments with J. Lanman and J. Allum, I found that the gaze (the sum of eye and head

movements) remained on a moving target just as accurately when the head was free as it did when the head was fixed. The eye movements, however, differed greatly in the two conditions. With the head free, the eyes remained fairly stationary in the center of the orbit, and smooth pursuit was accomplished almost entirely by the head movement system. To investigate the mechanism for coordinating eye and head movements during smooth pursuit, I used a brake to suddenly and unexpectedly arrest head movements during tracking. The eye movement accelerated within 15 milliseconds after the brake was applied. This acceleration was so fast and so accurate that the gaze continued almost uninflected, with no detectable change in retinal error. Acceleration of eye movements must be caused by the release of a signal representing target velocity in space or gaze velocity from the opposing action of vestibular input, because the latency of the visual loop is too long and the neck afferents are too slow (70 to 80 milliseconds) and has a very low gain in monkeys. Presumably this signal drives the circuits of eye and head movement. During normal smooth pursuit with the head free, the head must follow this command with a lag that depends on the activation time of the neck musculature and on the amount of prediction involved in the pursuit strategy. The eyes, however, appear to receive not only the postulated smooth pursuit signal but also a signal generated by the activation of the vestibular system. This latter signal specifies movements counter and proportional to the head movement. The combination of the two signals in some part of the oculomotor system results in an eye movement with an amplitude nearly equal to the difference in amplitude between the target and head movements. This difference is small, so smooth pursuit with eyes and head consists mainly of head tracking.

Little is known about the derivation of the postulated signal representing target velocity in space or gaze velocity. Visual information certainly plays an important role in generating it, a role recognized by the many investigators who have considered a retinal-slip servo model for smooth pursuit. There is, however, a growing body of information suggesting that retinal slip is only one of several inputs driving eye movements during smooth pursuit.

Possible single cell correlates to the postulated central representation of target velocity or gaze velocity have been found. Miles and Fuller recorded from Purkinje cells in the monkey flocculus during smooth pursuit and found cells that fired at a rate proportional to the target's velocity in space whether or not the head was moving. Because the gaze is very nearly on target during smooth pursuit, these cells may encode either target velocity in space or gaze velocity. These physiological findings are complemented by the results of lesions and psychophysical investigations. On the basis of one such study, my colleague, Larry Young, recently proposed that a central process, identified as "perceived target velocity," is the stimulus for smooth pursuit.

Plastic Changes in Central Organization of Eye–Head Coordination

In collaboration with J. Dichgans, I have shown that bilateral elimination of the vestibular apparatus in monkeys and humans profoundly disturbs eye–head coordination. For the first few days after surgery, the animals attempt to bring the fovea to the target and maintain fixation in several ways: by delaying initiation of the head movement, by relying almost exclusively on head movement, or by greatly reducing the velocity of head movement. Although these patterns are present for only a short time, they show that there is great flexibility in the programming of eye and head movements.

The process of recovery is already evident at the end of the first postoperative week, and in monkeys ocular compensation equivalent to abut 50% of the amplitude of the head movement is present by the 10th day. Ordinarily ocular stabilization continues to improve until it reaches 90% of the normal value at the end of the first month.

Several compensatory mechanisms that stabilize the eyes during head movement in humans and monkeys account for this impressive recovery. One of the most important is the potentiation of the cervico-ocular reflex. In humans and normal monkeys, the cervico-ocular reflex contributes little to ocular stabilization because the vestibuloocular reflex ensures gaze stability during rapid head movements. In chronically labyrinthectomized monkeys and humans, however, the gain of the cervico-ocular reflex during passive head movement increases to about 0.3. A phasic enhancement of this loop during active head turning has also been observed. In patients with bilateral loss of vestibular function, the gain of the cervico-ocular reflex is also significantly enhanced.

Centrally programmed compensatory eye movements have also been found to contribute to ocular stabilization during active head turning in vestibulectomized monkeys. In vestibulectomized monkeys, though, the oculomotor system is capable of taking over (albeit in a crude and incomplete way) functions previously elicited by afferent vestibular activity. I have shown that this eye movement persists after cervical deafferentation and is thus not due to feedback from any remaining peripheral afferents, such as joint afferents. It therefore represents a new functional property of the central oculomotor system.

We have shown that the central oculomotor mechanism responsible for compensatory eye movements acts according to information transmitted from the head programming center. It follows that recovery of ocular stability in vestibulectomized monkeys entails not only a reorganization of motor function—the generation of compensatory eye movements—but also the development of functional connections between motor centers (head and eye) that are ordinarily functionally independent. Humans with defective labyrinthine systems in whom head movement was stopped during gaze

changes also showed evidence of central programming of compensatory slow movements.

The third compensatory mechanism in chronically vestibulectomized monkeys involves a recalibration of saccadic eye movements with respect to retinal error signals. We found that the amplitude of saccades with the head free was significantly decreased in such monkeys. This mechanism is useful in preventing gaze overshoot and compensating for inadequate compensatory slow movement. In humans and monkeys, the saccades fell short of the target when the head was unexpectedly blocked but were accurate (in the same subjects) when the head was persistently immobilized.

In conclusion the studies in monkeys and humans have shown that the recovery of ocular stability is a complex process entailing parallel development of functional properties along three different lines: the potentiation of the cervico-ocular reflex, the central programming of compensatory eye movements, and the recalibration of the relationship between retinal error signals and the amplitude of the saccade.

The Control of Limb Posture

In parallel with the study of the eye–head coordination, I investigated the mechanisms related to the termination of a voluntary movement and the acquisition of a stable posture. As a model system, Polit and I selected the movements of the head and the arm of the monkey. To gain some understanding of the actual processes underlying posture we disturbed centrally initiated head movements by applying loads; our goal was to observe the effect of the resulting proprioceptive response on the final position of the head. When we applied a constant torque load whose effect extended beyond the dynamic phase, we observed a constant degree of head undershoot. Although the constant load was being applied, there was an increase in muscle spindle discharge, indicated by an increase in EMG activity. Presumably, tendon organ activity also increased, and there was a modification of postural information from joint receptors. However, in spite of these changes in the flow of proprioceptive activity, the head reached its "intended" final position after the constant load was removed. This final head position was equal to (on average) that reached when the load had not been applied, suggesting that the program for final position was maintained during load application and was not readjusted by proprioceptive signals acting at segmental and suprasegmental levels. We concluded that the central program establishing final head position is not dependent on a readout of proprioceptive afferents generated during the movement but is preprogrammed.

To test this hypothesis further, we investigated the way in which our monkeys reached final head position when they were deprived of neck proprioceptive feedback in addition to visual feedback. The goal here was to observe how monkeys moving their heads in an "open-loop" mode dealt with

a constant torque applied during centrally initiated movements. We showed that following the unexpected application of a constant torque load at the beginning of a visually triggered movement, the head attained a posture short of its intended final position. Again, the position that the head attained after removal of the constant torque was found to be statistically equal to the position that the head reached when the load was not applied. These results indicate that the behavior of the motor system with respect to head posture is the same before and after deafferentation.

The result of this series of experiments contributes to our understanding of the mechanism whereby movement is terminated and a newly acquired position is maintained. If we assume that the "program" for head movements and posture specifies a given level of alpha motoneuron activity to agonist and antagonist muscles, and that the firing of these neurons will determine a particular length–tension curve in each muscle, then we must conclude that the final resting position of the head is determined by the length–tension properties of all of the muscles involved. This hypothesis explains the head undershoot when a constant load is applied and the attainment of the intended final head position following the removal of the load. Although the process of selecting a new equilibrium between the length–tension properties of agonists and antagonists should result in movement and the attainment of a new head position, it should be clear that our experiments did not rule out the presence of other parallel processes.

In a complementary set of experiments involving arm movement, we extended the previously described findings on the final position of the head. Adult rhesus monkeys were trained to point to a target light with the forearm and to hold the arm in that position for about 1 second to obtain a reward. The monkey was seated in a primate chair and its forearm was fastened to an apparatus that permitted flexion and extension of the forearm about the elbow in the horizontal plane. A torque motor in series with the shaft of this apparatus was used to load the arm. The experiments were conducted in a dark room to minimize visual cues; at no time during an experiment was the animal able to see its forearm. At random times, we displaced the initial position of the forearm. In most cases, the positional disturbance was applied immediately after the appearance of the target light and was stopped just prior to the activation of the motor units in the agonist muscle. Hence, when the motor command specifying a given forearm movement occurred, the positional disturbance had altered the length of the agonist and antagonist muscles, and the proprioceptive stimulation resulting from this disturbance had altered their state of activation. In spite of these changes, the intended final arm position was always reached; this was true whether the torque motor had displaced the forearm further away from, closer to, or even beyond the intended final position. To evaluate the proprioceptive reflex activity we retested the monkey's pointing performance after it had undergone a bilateral C1-T3 dorsal rhizotomy. Remarkably, we could elicit the

pointing response very soon after the surgery (within 2 days in some of the animals). The forearm was again displaced (at random times) immediately after the appearance of the target light and released just prior to the activation of motor units in the agonist muscles. Because the arm was not visible to the animal and the proprioceptive activity could not reach the spinal cord, the arm reached its intended final position "open loop." The fact that we never observed any sign of reflex response or reprogramming in the EMG activity corroborates this supposition. We found that the final arm position was reached even when the initial position was displaced. This finding suggests that what is programmed is an intended equilibrium point, resulting from the interaction of agonist and antagonist muscles.

Although we had detected a process underlying arm and head movement, we were aware that there were other processes that occurred during the movement. It is quite clear, for instance, that the head (or arm) movements that monkeys use to reach a given position can vary in velocity. Consequently, the mechanism by which an intended posture is achieved must coexist with a mechanism specifying intended head (or arm) velocity. Second, the successful execution of the hypothesized "programs" in the deafferented animal is contingent upon the animal's knowing the position of the arm relative to the body. Whenever we changed the usual spatial relationship between the animal and the arm apparatus, the monkey's pointing response to the target was inaccurate. The dramatic inability of the deafferented monkey to execute accurate pointing responses in an unusual postural setting underscores the great importance of afferent feedback in the control of movement.

Trajectory Formation: The Equilibrium Point Hypothesis

The observation that posture is maintained by the equilibrium between the length–tension properties of opposing muscles led to the idea that movements result from a shift of the equilibrium point caused by a change in neural input. Around 1980 investigators of motor control had become increasingly aware of the computational complexities in the production of muscle forces. Some proposed that the CNS derives a motion of the joints from the desired path of the end point (inverse kinematics) and that it then derives the forces to be delivered to the muscles (inverse dynamics). The idea that the CNS performs these inverse computations implies that it can somehow estimate precisely limb inertias, center of mass, and the moment arm of muscles. Small errors in the estimation of these parameters can result in inappropriate movements. Robotic experience with similar approaches has shown that inertial parameter errors as small as 5% can result in instability. Most motor control investigations regard this type of computation as rather unrealistic. As an alternative, we and others proposed a different solution to the inverse dynamics problem: the equilibrium-point hypothesis.

The equilibrium-point hypothesis was first proposed by Feldman (1966), who viewed joint posture as an equilibrium resulting from the length-dependent forces generated by agonist–antagonist muscles. A key feature of the equilibrium-point hypothesis is that muscles have spring-like behavior. Experimental evidence has indicated that muscles behave like tunable springs in the sense that the force they generate is a function of their length and neural activation level. The force–length relationship of individual muscle fibers was studied by Gordon and his colleagues, who related the development of tension at different muscle lengths to the degree of overlap between actin and myosin filaments. This overlap limits the formation of cross-bridges. The increase in muscular stiffness observed when the motoneuronal drive increases is considered a direct consequence of the generation of new cross-bridges.

A central postulate of the equilibrium-point hypothesis is that the CNS generates a temporal sequence of signals that specify, at all times, an equilibrium position of a limb and the stiffness of the muscles acting on the limb. Although the terminology of the equilibrium-point hypothesis is firmly rooted in the literature, the term *equilibrium position* was a source of some confusion. We used the term in the following sense: It is the location at which the limb would rest if the centrally generated commands were "frozen" at any given value and the limb were free to move in the absence of external loads or forces. In the presence of static external loads or forces, the actual equilibrium position of the limb, will in general differ from this position. We introduced the term *virtual position* to distinguish the two. A time sequence of central commands gives rise to a time sequence of virtual positions, which is called a "virtual trajectory." Evidence supporting this important hypothesis has been provided by three sets of experiments, which I will briefly summarize here (Bizzi et al., 1984). The movements used in these experiments were single-joint elbow flexion and extension, which lasted approximately 700 milliseconds for a 60-degree amplitude.

The first set of experiments was performed in intact monkeys and in those deprived of sensory feedback. The monkey's arm was briefly held in its initial position after a target that indicated final position had been presented. Then, the arm was released. It was found that movements to the target were faster than control movements performed in the absence of a holding action. It was found that the initial acceleration after release of the forearm increased gradually with the duration of the holding period, reaching a steady-state value no sooner than 400 milliseconds after muscles' activation. These results demonstrated that the CNS has programmed a slow, gradual shift of the equilibrium position instead of a sudden, discontinuous transition to the final position.

The same conclusions were supported by a second set of experiments in which the forearm was forced to a target position through an assisting torque pulse applied at the beginning of a visually triggered forearm movement.

The goal of this experiment was to move the limb ahead of the equilibrium position with an externally imposed displacement in the direction of the target. It was found that the forearm, after being forced by the assisting pulse to the target position, returned to a point between the initial and the final position before moving to end point.

This return motion was caused by a restoring force generated by the elastic muscle properties. Note that if muscles merely generated force or if the elastic properties were negligible, we would not have seen the return motion of the limb. Because the same response to our torque pulse was also observed in monkeys deprived of sensory feedback, it was inferred that proprioceptive reflexes are not essential to the generation of restoring forces. Taken together, these results suggest that alpha motoneuronal activity specifies a series of equilibrium positions throughout the movement.

Finally, in a third set of experiments, the arm was not only driven to the target location, but also held there for a variable amount of time (1 to 3 seconds) after which the target light at the new position was activated. A cover prevented the animal from seeing its arm. After the monkey reacted to the presentation of the light, it activated the arm muscles to reach the target position. At this point, the servo that held the arm was deactivated.

The results were as follows. The arm returned to a point intermediate between the initial and the target positions before moving back to the target position. Note that during the return movement, requiring extension, flexor activity was evident. The amplitude of the return movement was a function of the duration of the holding action. If enough time elapsed between activation of the target light and deactivation of the servo, the arm remained in the target position upon release.

These observations provided further support for the view that motoneuronal activity specifies a series of equilibrium positions throughout a movement. If the muscles merely generated force during the transient phase of a movement, we would not have seen the pronounced return motion of the limb during flexor muscle activity.

The sequence of static equilibrium positions encoded during movement by the motoneuronal activity has been labeled a "virtual trajectory," to be distinguished from the actual trajectory followed by the limb (Hogan, 1984). The virtual trajectory is based on length–tension relationships under static conditions. By contrast, the actual trajectory is the observable result of the interaction between the elastic forces and other dynamic components such as limb inertia, muscle velocity–tension properties, and joint viscosity.

Because the biological actuators are springlike, the inverse-dynamics problem does not need to be solved. In fact, according to the equilibrium-point hypothesis, the CNS can express the desired trajectory of a limb directly as a sequence of equilibrium positions. Then the muscles' springlike properties transform the difference between the actual and the desired position of the limb into a springlike restoring force. The actual motions that result are

inexact but are produced without computing any dynamics. Consequently, there is no need to postulate neural structures to perform these complex computations.

Of course, the equilibrium-point hypothesis does not eliminate all computational problems; a pattern of neural activity may define a virtual trajectory, but there remains the formidable problem of how to select an appropriate pattern of neural activation to produce a desired virtual trajectory. Nevertheless, because it is based only on the static characteristics of muscles and their reflex connections and requires no knowledge of the dynamic parameters of the limbs (e.g., the inertias), this problem is significantly simpler than the direct computation of muscle forces or joint torques.

One major weakness of the equilibrium-point hypothesis is that it is difficult to test. The central concept is that posture and movement are subserved by the same processes. Static stability is arguably one of the defining requirements of posture; consequently, the equilibrium-point hypothesis makes the assumption that during movement as well as posture the limbs exhibit stability. Note that this is not a requirement for the motion of a mechanical system. Nor is it a fundamental requirement for a biological system, although it is physiologically plausible given the known springlike behavior of muscles and their reflex connections.

The theory that motor intentions are expressed and transmitted to the periphery using the virtual trajectory has direct implications for studies of cell discharge in the brain. The important point is that according to the theory, neither the forces generated by the muscles nor the actual motions of the limbs are explicitly computed; they arise from the interplay between the virtual trajectory and the neuromuscular mechanics. Hence, neither the forces nor the motions need be explicitly represented in the brain. If this theory is correct, then cell discharge studies might be better interpreted in terms of virtual trajectories and neuromuscular stiffness (or, more generally, impedance) than in terms of forces or motions.

Motor Learning, Generalization, and Consolidation

After investigating arm trajectory formation, I moved my research in the direction of motor learning. In collaboration with F. A. Mussa-Ivaldi and F. Gandolfo, I investigated how humans adapt to forces perturbing the motion of their arms. We found that as we adapt to the environment, the motor control system must learn to predict the perturbing forces that the limb will encounter so as to cancel them out while carrying out the desired movement. There are at least three ways for the motor control system to achieve adaptation. One is by representing the perturbing forces as a lookup table—that is, as a map that associates these forces to the states (positions and velocities) where perturbations have been experienced. An alternative is that the adaptation is not strictly limited to the visited states but to a small region around them. In this case, we would say that adaption is local to the

visited states. A third hypothesis is that the pattern of forces experienced locally generalizes over the entire arm's workspace. To find which alternative is most likely to be implemented by the motor control system, we investigated how subjects change their performance after prolonged exposure to a novel mechanical perturbation.

The protocol we used was designed by Reza Shadmehr and Mussa-Ivaldi when they were visiting my laboratory. Subjects were asked to execute arm movements toward visually specified targets. Once a baseline was established, force perturbations proportional to the movement velocity were applied to the subject's hand. Initially, the trajectories were significantly distorted by the applied forces. But after a period of practice within this altered mechanical environment, subjects recovered the original performance to a remarkable degree. In addition, when the mechanical perturbations were removed, the resulting trajectories displayed a compensatory response, which was a mirror image of the perturbed trajectory. This compensatory response has been termed "aftereffect." The presence of aftereffects is an indication that subjects adapted to the novel environment not by a generic strategy, such as by making their limb more rigid, but by generating end-point forces that exactly compensate for the applied perturbation.

Our experiments demonstrated that the motor control system builds a model of the environment as a map between the experienced somotosensory input and the output forces needed to counterbalance the external perturbations. Our results indicated that this map is local; it smoothly decays with distance from the perturbed locations.

Consolidation in Human Motor Memory

Learning a motor skill sets in motion neural processes that continue to evolve after practice has ended, a phenomenon known as "consolidation." In collaboration with T. Brashers Krug and Reza Shadmehr, we showed that consolidation of a motor skill was disrupted when a second motor task was learned immediately after the first. There was no disruption if 4 hours elapsed between learning the two motor skills with consolidation occurring gradually over this period.

Previous studies in humans and other primates have found this time-dependent disruption of consolidation only in explicit memory tasks, which rely on brain structures in the medial temporal lobe. Our results indicated that motor memories, which do not depend on the medial temporal lobe, can be transformed by a similar process of consolidation.

Neuronal Correlates of Motor Learning

In collaboration with R. Li and C. Padoa-Schioppa, we analyzed neuronal activity recorded in areas M_1, dorsal, ventral premotor, and supplementary motor areas in monkeys in a force field adaptation task. The animals adapted

to a viscous force field imposed upon their visually guided reaching movements—the perturbations of the arm trajectories decreased and eventually disappeared as the monkeys adapted to these force fields. When the force field was removed, the movement trajectories curved in the direction opposite of that observed when the force field was first imposed. The existence of this afteraffect suggested that the animals develop an internal model of the force field. By recording from the motor areas of the frontal lobe we identified two classes of memory cells—these cells encoded the adaptation through a change in forcing rate and special turning properties.

Because we were able to maintain the contact between cells and the microelectrode only for a single session, our results are only relevant to short-term learning.

The Problem of Controlling the Large Number of Degrees of Freedom of the Motor System

In the natural world, some complex systems are discrete combinatorial systems—they utilize a finite number of discrete elements to create larger structures. The genetic code, language, and perceptual phenomena are examples of systems in which discrete elements and a set of rules can generate a large number of meaningful entities that are quite distinct from those of their elements. A question of considerable importance is whether this fundamental characteristic of language and genetics is also a feature of other biological systems. In particular, whether the activity of the vertebrate motor system, with its impressive capacity to find original motor solutions to an infinite set of ever-changing circumstances, results from the combinations of discrete elements.

The ease with which we move hides the complexity inherent in the execution of even the simplest tasks. Even movements we make effortlessly, such as reaching for an object, involve the activation of many thousands of motor units in numerous muscles. Given this large number of degrees of freedom of the motor system we, as well as a number of investigators, have put forward the hypothesis that the CNS handles this large space with a hierarchical architecture based upon the utilization of discrete building blocks whose combinations result in the construction of a variety of different movements. In particular, investigators influenced by the artificial intelligence perspective on the control of complex systems have argued for a hierarchical decomposition with modules, or building blocks, as the most effective way to select a control signal from a large search space.

In the last few years, my colleagues and I have asked a specific question: Are there simple units that can be flexibly combined to accomplish a variety of motor tasks? We have addressed this fundamental and long-standing question in experiments that utilize spinalized frogs, freely moving frogs and rats. With an array of approaches such as microstimulation of the spinal

cord, N-methyl-D-aspartate (NMDA) iontophoresis, and an examination of natural behaviors in intact and deafferented animals, we have provided evidence for a modular organization of the frog's and rat's spinal cord. A "module" is a functional unit in the spinal cord that generates a specific motor output by imposing a specific pattern of muscle activation. Such patterns, in which a group of muscles are activated in a fixed balance, have previously been considered as muscle "synergies." Other investigators have generated corroborative evidence in cats. A clear-cut example of a recombination of synergies is from locomotion with the different limb central pattern guidelines (CPGs). Each CPG can operate independently, but the four-limb CPG can also be combined in different patterns as in a walk, a trot, or a gallop.

Recently, our laboratory has developed a novel method to identify muscle synergies with help of a computational analysis. This approach was first used by Tresch et al. (1999) who described the muscle activation patterns evoked from cutaneous stimulation of the hind limb in spinalized frogs.

The Construction of Movements with Muscle Synergies

For a long time, investigators have recognized that one of the basic questions in motor performance is whether the cortical motor areas control individual muscles or make use of synergistically linked group of muscles. Given that no natural movement involves just one muscle, any motor act, a fortiori, involves a "muscle synergy," the question then has been whether the synergistic activation of muscles derives from a fixed common neural drive or is merely a phenomenological event of a given motor coordination.

Despite the history of this issue, the vast literature on this question indicates little consensus either for fixed synergies or for individual control of muscles.

Even though most investigators doubt the existence of fixed synergies, they are nevertheless reluctant to accept the idea that a separate control signal must be computed for each muscle to achieve the appropriate movement. Various alternative mechanisms have been suggested such as hierarchical control. According to these investigators there is a hierarchy of parameters or strategies that are controlled in any motor act. Once the strategy is chosen a coordinated pattern of muscle activity is selected, but the muscle groupings are not considered to be fixed—they are formed and reformed each time.

Summing up, there is little doubt that the issue of muscle synergies has remained unsettled. However, there is a reason for this predicament—the approaches that have been used to investigate this issue have been based on correlation methods, which in this case are less than ideal for settling the muscle synergy question. The recent introduction of novel computational procedures has opened a different way to approach the issue of synergies. In 1999, Tresch and collaborators developed a variety of essentially similar

computational methods to extract synergies from the recorded muscle activations. In general, these methods try to decompose the observed muscle patterns as simultaneous combinations of a number of synergies. This decomposition is obtained using iterative algorithms that are initialized with a set of arbitrary synergies. The nonnegative weighting coefficients of these arbitrary synergies that best predict each response are then found. The synergies are then updated by minimizing the error between the observed response and the predicted response. This process is then iterated until the algorithm converges on a particular set of synergies. The algorithm extracts a set of synergies and the weighting coefficients of each synergy used to reconstruct the EMG responses.

Note that there are a number of factorization algorithms to assess the hypothesis that motor behavior might be produced through a combination of a small number of synergies. Tresch and his colleagues have compared different algorithms and found that, in general, most of the algorithms used to identify muscle synergies perform comparably. In particular, nonnegative matrix factorization, independent component analysis, and factor analysis performed at similar levels to one another.

In experiments we have evaluated this issue by examining several motor behaviors in intact, freely moving frogs. We recorded simultaneously from a large number of hindlimb muscles during locomotion, swimming, jumping and defensive reflexes (d'Avella and Bizzi, 2005; d'Avella et al., 2003), and we have shown that linear combinations of a small number of muscle synergies may be a strategy utilized by the CNS to generate diverse motor outputs. Furthermore, most of the synergies used for generating locomotor behaviors are centrally organized, but their activations might be modulated by sensory feedback so that the final motor outputs can be adapted to the external environment. Such an organization might help to simplify the production of movements by reducing the degrees of freedom that need to be specified by providing a set of units involved in regulating features common to a range of behaviours

Conclusions

I have been lucky in my career. It was a privilege to have met in my formative years outstanding scientists like Moruzzi, Evarts, Rita Levi-Montalcini, and Hans Lukas Teuber. As I settled at MIT, I was fortunate to conduct my research in collaboration with a superb group of students, postdoctoral fellows, and colleagues. They vastly enriched the scope of my investigations on the motor system—whatever I accomplished would not have been possible without them.

Early on, my research was conducted predominantly through collaborations with postdoctoral fellows with degrees in electrical or mechanical engineering or computer science. Vincenzo Tagliasco, Pietro Morasso, both from

the university of Genova, Italy, and Parvati Dev from the University of Massachusetts were all trained in bio-engineering and in my laboratory became involved in the study of motor coordination. As they left I started a long-lasting collaboration with Neville Hogan from the MIT Department of Mechanical Engineering. Aware of the risks of too much engineering and wishing a healthy balance between biology and the hard sciences I then invited Johannes Dichgans, a young German trained as a neurologist in Freiburg, to join my laboratory.

As I moved from the investigations of motor coordination to the study of the motor programs underlying arm trajectory formation, my collaborators were graduate students Andreas Polit, Doug Whittington, and Joe McIntyre, postdoctoral fellows William Chapple, Francis Lestienne, William Abend, Neri Accornero, and again my colleague Neville Hogan.

During the 1990s when I started to investigate the modular organization of the motor system, Sandro Mussa-Ivaldi, now a professor at Northwestern University, and Simon Gizster provided crucial input to the development of this project. Gerry Loeb and Philippe Saltiel joined the modularity theme later. Incidentally, we are still working on modularity, and I'd like here to acknowledge the contributions of Matt Tresch, Andrea d'Avella, Vincent Cheung, Simon Overduin, Andrew Richardson, and Jin-Sook Roh.

Next to modularity my current interest is motor learning. My involvement in investigating this topic began when Sandro Mussa-Ivaldi and Reza Shadmehr developed a way to evaluate quantitatively the acquisition and retention of a simple motor task in normal volunteers. This important study got everybody excited and spawned three new lines of research that are still being pursued in my laboratory. One theme began when Brasher-Krug and Reza Shadmehr investigated the time course of consolidation of motor memories in humans. This topic was then recently pursued by Simon Overduin who was able to specify critical behavioral features necessary for the establishment of consolidation. Working with patients affected by cortical strokes, Maureen Holden explored the power of augmented feedback using virtual environment to promote reprogramming of motor functions. In our second line of work we have focused on a description of the pattern of discharge of cortical neurons located in the primary motor, premotor, and supplementary motor areas of the monkey. Francesca Gandolfo and Brian Benda began this work that was then continued by Ray Li and Camillo Padoa-Schioppa and Andrew Richardson. The results of this extensive investigation of motor cortical areas revealed the presence of a population of cortical neurons that changed their firing rate during learning and then retained these changes afterward. On the basis of this outcome we felt we could label these cells as "memory neurons." However, because current techniques did not allow us to record from the memory cells for more than a few hours, it remains to be seen whether this label may or may not apply. Other interpretations are possible as shown by Uri Rokni in a modeling study based on the cells we had recorded.

Although the collaborators I have just mentioned contributed in fundamental ways to the scientific productivity of my laboratory, I want also to gratefully mention that the indispensable financial resources came mostly from the NIH granting system, which provided my laboratory with more than 40 years of uninterrupted funding. Last but not least I want to acknowledge Margo Cantor, who for many years provided indispensable technical assistance in my laboratory, and Charlotte Potak, whose administrative expertise in the office and laboratory has been invaluable.

Finally, considering more than 40 years of research on the motor system, my own and that of others, I believe that the study of action systems has an exciting and a scientifically rewarding future. By now a lot of basic, sometimes pedestrian, but useful work has been done, and we have reached the point where the next generation of investigators might attack what I consider the major challenges in this area: generalization and motor learning.

To me the most wonderful and astonishing feature of the motor system is its capacity to learn a task in one context and perform it with competence in a variety of new situations. Understanding this problem is hard, no doubt, and we sorely need theoretical work to explore a variety of alternative experimental models. Of course the system that provides generalization has to retrieve the signals representing the task from circuits that have been changed by learning, but are inherently unstable as the recent data by Robert Ajemian seem to indicate. This question of synaptic instability is central to learning, consolidation, and retrieval. To investigate these problems, new theoretical models and probably new recording techniques that will permit long-term tracking of the behavior of neurons need to be developed. In addition, we should also explore whether knowledge of the genes that are involved in motor learning might generate new investigative tools. Hard to say, but one thing is certain. The next generation will need a good dose of optimism and luck to tackle these tough problems.

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