Joaquín Fuster

Born:

Barcelona, Spain
August 17, 1930

Education:

University of Barcelona, M.D. (1953)
University of Granada, Ph.D. (1967)

Appointments:

Assistant and Associate Researcher, Anatomy and Psychiatry, University of California at Los Angeles (1960–1963)
Visiting Scientist, Max-Planck Institute, Munich, Germany (1962–1964)
Member, Brain Research Institute, UCLA (1961–present)
Member, Neuropsychiatric Institute, UCLA (1962–present)
Research Anatomist and Psychiatrist, UCLA (1963–1967)
Professor of Psychiatry, UCLA (1967–2002)
Professor Emeritus of Psychiatry (2002–present)

Honors and Awards (Selected):

Career Investigator Award, NIMH, 1960
Senior Scientist Award, NIMH, 1990
Ojemann Lecturer, University of Iowa, 1995
Member of Honor, Spanish Royal Academy of Medicine, 1997
Signoret Prize, University of Paris, 2000
Fyssen International Prize, Paris, 2000
Doctor "Honoris Causa," University of Alicante, Spain (2004)
Goldman-Rakic Prize for Cognitive Neuroscience, NARSAD (2006)
George Miller Prize, Cognitive Neuroscience Society (2007)
Doctor "Honoris Causa," Autonomous University of Madrid (2009)
Geschwind Lecturer, Harvard University (2009)
Woolsey Lecturer, University of Wisconsin (2010)
American Academy of Arts and Sciences (2010)
Segerfalk Lecturer, University of Lund, Sweden (2010)

Joaquín Fuster has devoted his research career to the cognitive neuroscience of the cerebral cortex. His principal contributions have been to the physiology of the frontal lobe in cognition. He was the first to discover "memory cells" in the prefrontal cortex, and later in the temporal and parietal cortices. These cells and their connections form cortical networks that, when activated, constitute the functional substrate of working memory, an executive function essential for goal-directed behavior, language, and reasoning. Studies of those networks in the well-defined experimental conditions of working memory are making it possible to characterize the organization of long-term memory and its dynamics in the perception/action cycle. These studies substantiate the new network paradigm of cortical memory that Fuster has proposed.

Joaquín Fuster

Barcelona

Everybody loves Barcelona, for its light, its architecture, its art, its food, and its people—Cervantes has Don Quixote call the town "the archive of courtesy." Nestled in northeastern Spain between the Mediterranean and a low mountain range, the capital of Catalonia has been for centuries the main commercial and cultural gate to Spain, from land and sea. Catalan is a separate and distinctive language, now with a rich literature, which is closer to French than it is to Spanish; it derives from the vernacular Latin spoken by early merchants along the Via Augusta, the coastal route that linked Rome with Hispalis (Sevilla) and Gades (Cádiz) in the south of the Iberian Peninsula.

Barcelona is one of the most progressive European cities. The Spanish industrial revolution began there, notably with textile mills—as in England. With expanding industry and commerce, the end of the 19th century brought great wealth to the city, and an exceptionally enlightened and philanthropic bourgeoisie. With prosperity also came a large proletariat and periodic civil unrest, especially acute in recessions. Bakunin, the notorious Russian anarchist, made Barcelona one of his favorite venues. The Spanish Civil War (1936–1939), like other national cataclysms in Europe, was a direct result of the lingering Great Depression that began in Wall Street, not of ideologies, class wars, or nationalisms (Basque, Catalan, or other).

In wealthy Barcelona, all kinds of cultural institutions flourished: the University with its prestigious professional schools, the Music Conservatory, the Opera House (Teatro del Liceo), second to none in the world, the School of Fine Arts, literary assemblies of all sorts, and several technical schools. Pompeu Fabra, the foremost Catalan grammarian—my wife's great-uncle—was an engineer; hence, his Catalan Dictionary is better for technical terms than the Dictionary of the Spanish Royal Academy of Language. Today there is a technological university named after him. All those institutions, coupled with the cosmopolitan cultural climate that a large harbor promotes, made Barcelona the permanent or temporary home for scores of famous artists, among them Ramón Casas, Pablo Picasso, Pau Casals, Salvador Dalí, and Joan Miró. The most distinguished Barcelonese of them all was undoubtedly Antoni Gaudí, the pioneer of modernist architecture, who greatly inspired Gropius, Le Corbusier, and Frank Lloyd Wright, among many others. Medicine was one of the thriving professions. The Medical School had always a prestigious faculty that trained many world-renowned medical scientists and physicians. Cajal was chairman of Histology in Barcelona for 5 years

(1887–1892). According to himself (Cajal, 1923), there he made his most important scientific contributions, including the neuron theory.

I was conceived on the last month of the Roaring Twenties, on the year in which Barcelona hosted the World Exposition (1929). I have never attempted to associate the events surrounding my birth with the future course of my life—except for the fun of "what if." The reality was, however, that after those events the world economy went downhill and Spain entered a long depression, followed by a terrible 3-year war and 40 years of dictatorship. These were hardly favorable conditions for a young man to enter a scientific career. In any case, it was written in the stars—or genes—that this one, the oldest of five siblings, would become a doctor, like others in the family.

Indeed, my family was steeped in medical tradition. I have lost count of the number of physicians in our last four generations—somewhere between 15 and 20, several in academia. Included in the list are my grandfathers, my father, my brother, and my son. My maternal grandfather, Professor Carulla, was a truly remarkable person. A man of humble origin who by humble jobs paid his way through pharmacy and medical schools at the University of Barcelona, of which, after a distinguished career as professor of medicine, he eventually became the Rector (president), and founder of the Medical School Hospital. Throughout his career he was consumed by a burning interest in education at all levels. Even while occupying the highest academic post in higher education, my mother told me, he would travel from village to village in the Pyrenees, sometimes on mule-back, inaugurating elementary schools ("here it all begins," he used to say). For his accomplishments, the king Alfonse XIII made him marquis. They say he was slated to become Spain's minister of education when he died, in 1923.

On that same year my father graduated from medical school (so did my father-in-law). After a brief stint in forensic medicine, my father decided to enter psychiatry. Following his training in that specialty, he served in several public mental-health institutions in Barcelona; eventually he would become the director of two of them in succession. After the Spanish Civil War, and a brief political clearance, for he had served in the medical corps of the army of the Republic (the losers), my father opened a small private psychiatric hospital in a large home that we rented in the outskirts of Barcelona. It was in the early 1940s and thus I was about to enter puberty. For reasons that had to do as much with economics as with quality control (my mother was a keen overseer of the business), our family lived with the patients, with whom we shared kitchen, dining table, and a sumptuous garden. It was a peculiar arrangement for us children, which for me lasted into late adolescence. I know another neuroscientist, Torsten Wiesel, who lived through an almost identical experience in his father's psychiatric hospital up in Sweden. For my part, I have frequently told my psychiatric residents—tongue-in-cheek, of course—that I started my residency at an early age, and under a superb attending physician. . . .Indeed, my father, who in due time became university chairman, was widely reputed to be one of the best teachers of psychiatry in Spain.

Feelers from Tyrol

After medical school and more formal psychiatric training, my interests began to focus on the brain. I was in Innsbruck (Austria), undergoing some of that training, when the "brain bug" bit me hard. The bug piggybacked on my learning of English, which I was doing on the side to enlarge my knowledge of languages (I am more or less proficient in six). I became fond of practicing my new language reading issues of the *Journal of Neurophysiology* in the University of Innsbruck library. There I stumbled on the papers of H. W. Magoun and his colleagues on the reticular formation of the brain stem and its role in arousal. I was utterly fascinated by the subject and promptly discovered in my mind all kinds of psychiatric implications of it. With my poor English and zero experience with animal research, my understanding of the methodology was sadly deficient. I felt it was good enough, however, to pose a reasonable research question to H. W. Magoun, and even to dare asking for his tutelage to try to find the answer. Two excerpts of my correspondence with him illustrate my youthful impudence and naïveté, as well as his indulgence. I print them here because they undoubtedly constitute my first practical step into a research career.

Innsbruck, 8.6.1954

Dear Professor Magoun,

. . . . . .Quite convinced of the importance of the role of the brain stem reticular formations in the psychological and somatic manifestations in the circular mental diseases, I would be interested in undertaking some investigation work in order to study the function of those reticular formations in the maniac [*sic*] and melancolic [*sic*] states. Would it be possible, for instance, to measure with oscillography the latency, the speed and other characteristics of the EEG "arousal response" in both kinds of patients? . . .Could I work here [at UCLA] under your direction?. . .

Los Angeles, 9.9.1954

Dear Dr. Fuster:

The program of investigation under way in Los Angeles is almost completely. . .on the electrical activity of the brain of experimental animals. However, many aspects of the work are of interest for psychiatry. . .Should you be interested in devoting a year to this kind of activity, we should be happy to have you with us. . . . .

Very sincerely yours,

H. W. Magoun, Professor and Chairman

That was good news. I did not leave Austria, however, without attempting to do some preliminary research on mood and "reticular formations." There is an old psychophysical test called the *Klopftest* or Tapping Test.

It measures the ability of an individual to maintain a rhythm by finger-tapping it on a table after having heard it from a metronome. I believe I reasoned that depressed patients would slow down the rhythm, whereas manic patients would accelerate it. This makes some sense by transposing to finger-tapping what patients of the two kinds do with psychomotor activities, including speech. Now, the reasoning with regard to arousal systems gets a little more tenuous. In any case, I proceeded with my low-cost project after having assembled what I thought was a reasonable sample of patients on the wards of the Innsbruck university hospital. Halfway through the testing, however, I learned for the first time that in research things do not always turn out as expected. On the patients I had examined until then, the anticipated correlation simply did not materialize, at least by using my pedestrian statistics, which I reckoned were sufficient for the purpose. I have never forgotten my shock when, at that point, my next test subject, a severely depressed patient, submitted himself to the procedure and, after hearing the standard rhythm, finger-tapped without the least deviation from that standard. He happened to be a member of the Zagreb Symphony Orchestra! That did it. Before redesigning the study, which I thought required at the very least the control of the musical education of each subject, I finished my fellowship and went back to Spain.

Del Amo Fellow to UCLA

Back in Barcelona, and encouraged by Magoun's letter, my first priority was to find a fellowship to come to America. I found the perfect one: a Del Amo Fellowship. Don Gregorio Del Amo (1858–1941) was a physician from northern Spain (Santoña) who, after graduating from Madrid University, went to Uruguay, and later Mexico, to practice medicine. In 1887 he came to Los Angeles, where he ultimately settled and married the daughter of Domínguez, a wealthy Spanish "hacendado." This gentleman owned the historical Rancho San Pedro (royal endowment from Charles IV), a huge property encompassing what is now occupied by several cities between the Los Angeles River and the Pacific Ocean, including most of current metropolitan Los Angeles. After becoming by inheritance the owner of the property, oil was discovered under it, in enormous quantities. Thus, Dr. Del Amo became a multimillionaire from the oil and land development revenues of the Del Amo Estate Company, which he founded. In 1906 he ceased to practice medicine to devote all his energies to business, which extended into banking (Union Bank). He also became a philanthropist, patron of the arts, and diplomat (General Consul of Spain in San Francisco). But never does a physician turned-something-else abandon completely his interest in medicine. Thus, Dr. Del Amo devoted much of his money to the advanced education of physicians. In 1929 (a year significant to me for another reason), he established the Del Amo Foundation in cooperation with the University of California at

Los Angeles (UCLA), the University of Southern California (USC), and the University of Madrid. Its mission was to provide Spanish and Californian medical graduates with the means (fellowships) to carry out advanced studies as foreign visitors in those universities. In 1955, armed with Magoun's letter, and after a couple of interviews in Madrid (with Jaime, the son of Dr. Del Amo, and a lawyer administrator of the Foundation), I was awarded a Del Amo Fellowship and travel money to the United States.

I crossed the Atlantic in the *Conte Biancamano*, a liner originally built in Scotland for the Italian Line, which during World War II had been seized by the U.S. Navy, converted into the *SS Hermitage*, and used for troop transport to European shores. One February day in 1956, 10 years after being stripped of guns and refurbished, the *Conte Biancamano* came to New York from Barcelona once more, this time with me on board. It was cold in the Great Apple, though not freezing as on the day before, during the boat's stopover in Halifax, where none of the good Canadian whiskey could be had to warm up, for it happened to be Election Day in Nova Scotia. In New York I took a plane almost immediately for sunny California.

I was received at the old LAX airport by Tom Haley, a UCLA neuropharmacologist, who was a good friend of Spain, of the Del Amo's, and of several other investigators in Magoun's cohort, which spanned across several departments. Tom Sawyer, the well-known neuroendocrinologist, was now the Chairman of Anatomy, and my first boss at UCLA. Through his office and the Foreign Student Housing office I was procured living quarters at a 5-minute walk from campus: a room in the home of a German professor of geography who was well traveled and spoke good Spanish ($50/month with breakfast).

The Reticular Formation

Robert ("Bob") B. Livingston, a professor of physiology originally from Yale (Fulton Laboratories) was my first scientific chaperon at UCLA. Bob was one of ("Tid") Magoun's collaborators in the discovery of the role of the brain-stem reticular formation in arousal. He procured me a lab in a temporary building (5F) near the recently constructed medical school and hospital complex. Assorted research and clinical facilities that for whatever reason did not fit in the new building were accommodated there. It was a curious place. Because years before 5F had served as the provisional Religious Conference Center of the university, it had a monastic structure, with a central quadrangular courtyard ("cloister") surrounded by corridors and outlying rooms ("cells"). Now it housed a hodgepodge of university facilities, none of which nowadays would be probably approved by any conceivable accreditation board: the outpatient psychiatric department with the Psychiatry chairman's office, an electronics shop, an animal vivarium with rodents, cats, and

monkeys, a couple of psychoanalysts' offices, a biochemistry lab, a steno pool, two neuropharmacology labs, a sociologist's office, and a couple of small rooms near one of the entrances for this neophyte researcher from Spain.

In one of the two rooms assigned to me there was a Wisconsin General Test Apparatus (WGTA) for monkeys that two of Bob's medical students had used for a behavioral study on visual discrimination, which eventually was designed to include neurophysiological research. It was supported by grants to H. W. Magoun, Bob Livingston, and Don Lindsley, professor of psychology, who was another member of the interdisciplinary Magoun's cohort. When I came, the two students were busy with their classes and it seemed to me that the monkey-behavior part of the project was still poorly defined in anybody's mind (I never read the grants). Anyway, the students were commissioned to teach me how to handle monkeys, which to that date I had only seen at zoos. They did that and also taught me the essentials of behavioral testing in the WGTA. Obviously catering to my interests and those of the group, I was being groomed for behavioral electrophysiology on monkeys, which no one else had yet done at UCLA. Now, more than a half century later, I still wonder how it had been possible that a young medical graduate with little more than good intentions, a few ethereal ideas, and a clinical nonresearch education was entrusted with that much responsibility—and given such a great opportunity. I think this would be now inconceivable anywhere. Perhaps my mentors were swayed by my "reticular enthusiasm," my coming from the country of Cajal, or my psychiatric training; in the "monastery" (so was 5F referred to in jest), the department of psychiatry, my specialty, was situated down the corridor from my lab. Of course, there may have been several reasons why the psychiatric connection worked in my favor. One of them was political, or epistemological if you will. Norman Brill, the chairman of psychiatry, like most every other chairman of psychiatry in the country at that time, was a "devout" Freudian psychoanalyst. A few months before, Percival Bailey, the dean of American neurosurgery (and father of one of Magoun's assistants), created a furor by lambasting psychoanalysis in front of the American Psychiatric Association. I suppose this young Spanish psychiatrist offered a little encroachment of the brain into psychiatry or a little "rapprochement" between brain science and psychiatry. It may have been both, for eventually Brill became my boss, and a good one at that.

The reality was that, in 1956, shortly after my arrival I had at my disposal a decent lab, a WGTA, an oscilloscope, a brain stimulator, and a bunch of monkeys. As to what to do with all that, and how to do it, it was left pretty much to my own wits. It seemed, however, that some kind of research on brain-stem reticular systems was expected from me, though it was left up to me to design it. (Of course, I had no trouble with that expectation!) Fortunately, in 5F, I encountered for the first time the key to academic success in the West: the spirit of "enlightened individualism" that David Starr Jordan,

the first president of Stanford University, had brought to the West Coast at the beginning of the century and that, ever since, reigns in all the academic institutions of this coast, from Vancouver to the Mexican border. That spirit encourages you to do freely what you want without command or supervision *if* you do it well, and *if* you avail yourself to others for mutual help and to serve a worthy common cause. This deviates a little from the European–Eastern U.S. model.

Before I ventured into physiology with carte blanche and minimal but expandable infrastructure, I decided to develop a more sophisticated test than the visual discrimination tests customarily conducted with the WGTA. Those were too crude for any neurophysiological metrics. My objective was to stimulate the midbrain reticular formation and thereby to facilitate some kind of fine and difficult perceptual performance. The issue in my mind was the reticular "control" of attention. My reasoning went like this: if its arousal system were stimulated in the wake state, an animal would have that extra arousal to be more alert and to better perform difficult discriminations.

In my search for a suitable behavior, I turned to touch, more precisely active touch (haptics). With a saw, a hammer, and nails, I modified the WGTA for tactile discriminations. In my new paradigm, the experimental animal had to reach with one hand above and beyond a wooden partition into a plastic bag hanging out of sight on the other side of the partition, palpate geometric objects in it, and choose one for reward. Throughout the procedure the monkey and the tester could not see each other. Soon I was disappointed to realize that stereometric discriminations by touch were very difficult for monkeys to learn, much more so than visual ones. Eventually I would learn that auditory discriminations are even more difficult.

Then, one day, one particular subject started to perform haptics at 100% level, all of a sudden though a little more slowly than in previous days; the animal's reaction time had gotten longer. Aha! I thought to myself, the learning curve is steeper than the books say, and the critical factor is "deliberation. . .". Not quite trusting my reasoning, I installed a little strategic mirror that allowed me to see the monkey though he could not see me in the dark. Discovery: on every trial, before reaching, the animal peeped through a nail hole in the partition, a leftover from my remodeling of the apparatus. That way, he could visualize the position of the objects in the transparent bag before reaching into it. He was using vision after all! It was the second methodological failure of my scientific career (the first had been with the Croatian musician). There would be others, and I would learn something from each and every one. That one taught me that monkeys were a lot smarter than I thought.

A Tachistoscope for Monkeys

Everybody, including my monkeys, was telling me to use vision to study attention. Then I remembered having read in a psychology book, back in

Spain, that the tachistoscope was an excellent instrument to test visual attention in the human. Could I build a tachistoscope for monkeys? It seemed a worthwhile challenge. But then, my monkeys were accustomed to visually discriminating pairs of objects presented simultaneously side by side on a tray in the WGTA. What if on every trial I cut the time of exposure of the objects to a fraction of a second, around the threshold for discrimination? I could make a tachistoscope out of the WGTA!

But there were a few problems. Obviously, I could not use a movable wood screen to limit the exposure; then also, how would I get the animal to compare two objects rapidly without shifts of gaze that would limit my control? I interposed a one-way screen between the monkey and the objects—and myself. Then the electronics technician in 5F built a light source (gas-filled tube) with length of illumination controllable down to the millisecond. I would illuminate the objects for a few milliseconds and let the animal choose the one on the right or on the left by sticking either hand through one of two trapdoors. I would make one of the objects the "correct" (rewarded) one and change the position of the two objects at random between right and left. After experimenting with several pairs of objects, I chose a couple of white objects that looked very much alike and served me well: a cone and a 12-sided pyramid of similar proportions (about 2 inches in height and 3 inches in base diameter). To the human observer, at minimal exposure (3–5 ms), the two objects looked identical, the pyramid exactly like the cone. I made of the cone the correct object for the monkey on every trial. As for the difficulty to visualize both objects simultaneously in a split-second, the monkey solved that for me: on hearing the warning sound before the flash lit the objects, he would look to the side of the screen where one of the objects was to appear. If it turned out to be the cone, he would launch his hand through the corresponding trapdoor and retrieve the morsel of apple under it. If it turned out to be the pyramid, he would reach with the other hand through the other trapdoor, inferring, correctly, that the cone was there with the piece of apple underneath. As expected, the trained animal made more errors as the exposure (flash) became shorter, and his reaction time became longer.

Five months after my arrival in UCLA, I had achieved my behavioral paradigm to test visual attention in the monkey. Now the goal was to stimulate the reticular formation during tachistoscopic performance. There was one serious environmental problem, however: noise, for my lab was not soundproof. Experiments on attention required complete silence or masking noise. I used the latter, but sometimes it did not suffice, because the corridor had a wooden floor and high heels were fashionable at that time with lady patients and secretaries. Thus, I conducted most of my experiments at night, on the weekend, or after-hours.

Electrodes had to be implanted in the brain, and I needed help to do it. I had never operated on animals and did not know how to use a stereotaxic

instrument. No one was doing stereotaxic surgery on monkeys at UCLA. Fortunately, at the collegial request of Bob Livingston and Tom Haley, the Killams came to my rescue. Keith and Eve Killam were two neuropharmacologists of Magoun's team who were doing drug research on reticular systems in "chronic" cats. They had extensive experience in stereotaxia with cats and rabbits. Not with monkeys. Yet, with the help of Olszewski's monkey stereotaxic atlas, my first monkey was operated on in the Killams' lab. Under Nembutal anesthesia, several bipolar electrodes were implanted straight down into the midbrain and anchored to the skull. I took plenty of notes, for the next monkey was to be done by me in my lab, though under Keith's supervision.

Thus, finally I was ready to test my hypothesis. Would the electrical stimulation of the mesencephalic reticular formation make, as I predicted, my monkeys more alert, more attentive, to discriminate shapes briefly illuminated?

This time, after much toil, things seemed to turn out as predicted without major methodological problems. At long exposures, nothing happened; the animal had no problem discriminating the objects whether the electrical stimulus was on or off. At brief exposures (10–40 ms) under reticular stimulation, however, the animal made fewer errors and the electronic circuitry of the apparatus showed that its reaction time was shorter than without stimulation. In summary, the monkey saw better and reacted more quickly. That was my frequent observation with current intensity of 100–300 μA. Currents higher than that produced the contrary—disruptive—effects. Mild stimulation of other brain locations did not have the facilitating effect of the stimulated tegmentum of the mesencephalon.

Understandably, the data were welcome by my mentors but, as for anything apparently too good to be true, there were skeptics ("too much arousal," somebody said incredulously; I thought the same thing myself). I endeavored to make sure the initial data were reliable, adding monkeys to the study and consulting with many experts at UCLA, especially psychologists and statisticians. I would not publish anything about the matter until I was convinced beyond a reasonable doubt. I did not reach that point until the summer of 1957, with half a dozen monkeys. Then I decided to publish a preliminary report.

At about that time, the Department of Psychiatry offered me a research position, which I readily accepted. Lindsley, from Psychology, sent me a graduate student, Art Uyeda, a Nisei American, to help me consolidate my study and gather more data. I taught him how to handle monkeys and how to use my tachistoscope. That was helpful, for soon I was to leave the country for a while with an important mission.

With things going my way, I left my lab in Art's hands and went back to Barcelona to marry Elisabeth, my long-time girlfriend. Also, I would use the occasion to consult with my father before packing definitively for the States

to continue my research career. He supported the plan, though at first reluctantly, because with it he was to lose his psychiatrist son, whom he had done so much to train. He was, however, an open-minded liberal man with great confidence in biological psychiatry and nothing but contempt for the meager state of basic science under Franco's regime, even though clinical research and specialties, including psychiatry, continued to prosper in Barcelona, as they always had. Since Cajal, neuroscience's forte in Spain was, of course, neuroanatomy. Before the war, there had also been outstanding Catalan physiologists (Pi i Sunyer, Folch i Pi, Duran-Reynals . . .), some working on the brain and establishing prestigious schools around themselves. After the war, however, Cajal had died and many of his disciples (Lorente de Nó, Del Río Hortega, Achúcarro, among others) had emigrated to the Americas, and so had the physiologists. My father considered carefully my circumstances and, finally, with his characteristic firmness and conviction said to me laconically: "Go!"

A less determined acquiescence came from the Del Amo family, whose fellowships assumed, if not required, one's return to the home country to practice what he or she had learned abroad. My breach of expectation, if not contract, required upon my return to Los Angeles a lengthy explanation to Mr. Eugenio Cabrero, the secretary of the Foundation, who for the purpose invited me to lunch in the stodgy Athletic Club on 7th Street, near Union Bank—of which I believe the Del Amo family were majority owners at that time.

Debut in *Science*

At UCLA I was received with open arms, if nothing else because, despite my scientific immaturity, I was considered a kind of interdisciplinary bridge builder—and the only person potentially able to bring to fruition the monkey-behavior aspect of a Magoun-Livingston-Lindsley grant.

One year after my return, around the birth of our first child, Lisa, my first paper in *Science* (Fuster, 1958) was published: "Effects of Stimulation of Brain Stem on Tachistoscopic Performance." No other publication, other than perhaps years later the report on the discovery of memory cells, had such an impact on the course of my career. It was the first demonstration, in the behaving monkey, of a psychophysical effect of brain stimulation. Eventually, with the coauthorship of Dr. Uyeda, the phenomenon would be published with the complete results on a total sample of 14 monkeys (those were the days!). That work opened my access to federal funding, which at one level or another, I have maintained to the present day. My first federal grant was a Career Investigator Grant of the National Institute of Mental Health. The agency liked to support young biologically oriented psychiatrists. My *Science* paper eventually became a classic and was cited in several texts of physiological psychology (e.g., by Morgan, and by Thompson).

Anyhow, the tachistoscope lent itself nicely to pharmacological studies on visual attention and perception. Magoun's group included several neuropharmacologists to advise me on it. Because of the reported actions of lysergic acid on those functions in the human, and as an inducer of a model psychosis, I got a shipment of LSD-25 from Sandoz to test it on our monkeys performing the task. The substance produced deficits that were remarkable only for the minuteness of the doses necessary to produce them (single-digit microgram-range). Because the drug was a hallucinogen, Magoun arranged the visit to my lab by a famous LA resident writer, Aldous Huxley *(The Doors of Perception).* He came with his no less famous brother, Julian, who was visiting from the United Kingdom. I can still see the slim, tall, almost blind Aldous inspecting my monkeys at close range. All carried Spanish names of California places and towns: "Francisco," "Diego," "Jacinto," . . . I was introducing them to him, one by one, when we came to a little fellow with a large conical cement implant with electrodes on his head. Aldous looked at him closely, with curiosity and, before my pronouncing his name, he said in his gentle manner and British accent: "This must be San Luis Obispo, I suppose. . ."

Shortly after that, in Basel (Switzerland), a Sandoz scientist jumped to his death into the Rhine; a fellow scientist had surreptitiously laced his coffee with LSD. That led to an enormous scandal and a lawsuit against Sandoz (even though Sandoz's Hoffman, the discoverer of the drug's effects, had used it on himself). Coming on top of the disclosure of illegal experiments by secret agencies on both sides of the Iron Curtain, that incident contributed decisively to the embargo of the drug even for research purposes. By the time of my LSD publication (Fuster, 1959), I had used on my monkeys probably one of the last shipments of the substance from Sandoz Basel to the United States.

My more important agenda, however, was to clarify the mechanism by which reticular activation facilitated vision. Where in the nervous system did that facilitation take place? Whereas Cajal and Granit had found some slim evidence of centrifugal fibers from the brain stem to the retina, there was no clear physiological evidence of centrifugal output to the retina; in any event, it seemed unlikely that my phenomenon was mediated at the periphery of the visual system. Because monkeys were already then expensive, I decided to conduct my study of the matter on rabbits.

My monkey research continued at 5F, but the rabbit research proceeded in T-67, another temporary building, this one on the grounds of the Brentwood VA Hospital one mile away from campus. T-67 was a long (100 ft) hemicylinder of corrugated metal on stilts, adjoined orthogonally in the middle by another, shorter, hemicylinder. The building, which structurally had little more than the metal shell and a wooden floor (again!), had served for the housing and care of wounded soldiers from the War of the Pacific. Now, in 1959, it was on loan from the VA to UCLA Anatomy. In the long

section of the building there were four labs along a narrow side-corridor, and in the middle section (the stem of the "T") a couple of rooms for animals (cats and rabbits). I shared the makeshift lab-suite with three other neuroscientists: Carmine Clemente, John Green, and Ross Adey. The animal facility was manned by "Smithy," a jovial and efficient black Texan who was always in debt with all of us—albeit usually for modest amounts.

A Remote-Control Microdrive for Behavioral Neuroscience

In T-67, I dedicated myself to investigating in the rabbit the effects of electrical reticular stimulation on the responses of visual structures to optic stimuli. The question was, Where in the visual system did the reticular facilitation ("super-alertness") work? My project was to approach the question in striate cortex and the lateral geniculate body, the two major components of the central visual system. I was to use microelectrode single-cell recording and evoked field-potential recording. The animal had to be awake and comfortable. That was accomplished by placing it in a soft restraining hammock, which I designed, and by prior stereotaxic surgery under general anesthesia (Professor Sawyer, in Anatomy, had developed an excellent stereotaxic atlas for the rabbit). The purpose of the surgery was to implant electrodes in the reticular formation and visual structures, and a pedestal for a microelectrode carrier.

I designed and constructed the microelectrode carrier with the help of a precision machinist who had a lathe in his private West LA garage. It was a hydraulic microdrive with remote control, unlike anything available on the market at that time. Mine was destined to be the first microelectrode drive to be used for cognitive neuroscience in the behaving monkey. But first I was to use it in the rabbit. Herbert Jasper in Canada, without the benefit of remote control, had been the first to record single-unit spikes from the brain of monkeys performing simple conditioned movements (Jasper et al., 1958). Eventually, in the monkey, my system would offer me the advantage of advancing the microelectrode from afar without disturbing the animal's behavior with my presence.

The visual stimuli I used on my rabbits were far from ideal for testing the effects of attention on visual nerve cells. To assess visual neural responsiveness I used diffuse retinal illumination with light flashes. I was thus likely to miss any effect of attention on the reactions of cells to spatial contrast, so important for the assessment of visual attention. I did know, however, from the works of Hubel and Wiesel, in accord with the retinal works by Kuffler and Granit, that lateral geniculate and cortical cells with a central receptive-field response to "on" or "off" showed a comparable, though weaker temporal-contrast response to diffuse light-on or light-off. This response, I hoped, would be enough to reveal a cell's center-field characteristics and thus be sufficient to assess the effects of alertness, if not

attention, without necessity to control eye position and the receptive field responsiveness of each cell. It was an indirect way to assess effects of alertness on the cells' physiology without characterizing their feature-response properties. It should work reasonably well to test the physiology of the tachistoscopic effect, which was essentially based on temporal contrast anyway.

Johnnie Green taught me how to make metal microelectrodes and how to record with them. The results of reticular stimulation on a sample of striate cortical cells were quite convincing: in almost one-third of them, trains of mild electrical stimulation of the reticular formation produced cell-firing changes that mimicked the effects of light. Thus, "light-on" cells were excited by reticular stimulation, whereas "light-off" cells were inhibited by that electrical stimulus. Furthermore, when the electrical stimulus was made to coincide with the light, the effects of the two reinforced each other. Those effects—mimicking and synergy—provided an apparent explanation for the facilitating effects of reticular stimulation on tachistoscopic perception in the monkey. The increased alertness from that kind of brain-stem stimulation enhanced the temporal contrast in primary visual cortex; temporal contrast was, after all, at the foundation of tachistoscopic acuity.

That work was the subject of my second paper in *Science* (Fuster, 1961), in which I also used the opportunity to present my microelectrode recording method. At about that time, my good friend Fernando Reinoso-Suárez, chairman of Anatomy in Granada (Spain), was visiting with me on sabbatical for a few months. Together we embarked on a side-project to investigate the cortical synchronizing effects of reticular lesions. In Spain, as in several European countries, physicians are granted their medical license at the termination of medical school. They are not granted their doctorate, however, until they complete a short curriculum of advanced studies, conduct thesis research, and defend it before a tribunal in a Spanish university. Since I had already taken my doctorate classes before leaving for the States, Professor Reinoso offered me the possibility of using the work published recently in *Science* as the thesis material, expanded and translated, and of defending it in Granada. Thus, I eventually obtained my Ph.D. in neuroscience.

The rabbit reticular-stimulation project on visual evoked potentials was conducted in collaboration with Richard Docter, a psychology postdoctoral fellow (Fuster and Docter, 1962). We employed three methods to manipulate the activation of the reticular formation of the brain stem: electrical stimulation or amphetamine to enhance it, and a barbiturate to depress it. We stimulated the visual system with strobe flashes and measured the amplitude of potentials evoked by them. Our most consistent finding was the arousal-related changes in the amplitude of secondary (late, 150-300-ms latency) potentials in visual cortex. Similar potentials have been shown by other investigators to be enhanced in the human during visual attention. Likewise we found them parametrically enhanced by reticular activation and diminished by reticular depression.

It seemed thus quite clear that the facilitation of tachistoscopic acuity by stimulation of the mesencephalic reticular formation was exerted at the cortical level, not at the thalamic level or below. Only one other group of investigators, to my knowledge, had shown reticular influences on the visual physiology of the visual cortex. That was the group of Professor R. Jung and his colleagues in Freiburg, Germany. The influences they had demonstrated—in the cat—originated in the so-called thalamic diffuse reticular system, presumed to be the upward extension of the midbrain homonymous system. One of the members of that group was Otto Creutzfeldt, who was about to open a neurophysiology lab at the Max-Planck Institute for Psychiatry in Munich. In a short visit to UCLA in 1961, he and I got together and concluded that both could benefit from collaborating in his new lab. It appeared to me a splendid opportunity to acquire further expertise in visual physiology with a gifted pupil of Jung in a rich and brand-new setting.

Neuroscience Building Boom at UCLA

Indeed, at that time I felt I needed new lab quarters and further training in neurophysiology. Fortuitously, the Medical School and the Medical Center at UCLA were rapidly expanding, and neuroscience (the name did not yet exist) was undergoing a veritable explosion of new construction and facilities, particularly in all aspects related to mental health. There could not be a better place for a young research psychiatrist anywhere. At that time some of us benefited from a happy confluence of state and federal interests. The Department of Mental Hygiene of California, under Governor Edmund G. ("Pat") Brown, was to greatly expand or build anew two neuropsychiatric institutes, one in San Francisco (Langley Porter, UC) and the other in the UCLA campus, attached to their respective medical centers. Our institute was to consist of two sections, one for patient care and the other for basic research of clinical interest (now called "translational"). At the same time, Magoun's group was growing in size, productivity, and recognition. The group included investigators of several basic-science departments of the Medical School. They were attracting large amounts of money from the federal Public Health Service, especially the National Institute of Mental Health. And they were running out of research space in the new school.

After a series of high-level discussions and decisions involving the University and federal and state governments, of which I was never privy but could easily infer, the Brain Research Institute (BRI) was created, to be directed by Magoun, and the Neuropsychiatric Institute (NPI), to be directed by Brill. In effect, the NPI turned into the main quarters for the Department of Psychiatry, plus a mental hospital, with inpatient and outpatient facilities, and limited facilities for neurology and neurosurgery. The BRI, which had been originally conceived as the research part of the state's NPI (with too few of us wagging its tail!), turned into a full-fledged neuroscience

institute. Both would eventually consist of 10-floor adjacent towers annexed to the Medical Center. With the addition of the Reed Neurological Institute and the Stein Eye Institute, the entire UCLA medical complex would become the second largest building in the United States in floor surface (the Pentagon was the first). At the time of their creation, the University supported both institutes, NPI and BRI, with modest funding, mainly for faculty and staff. But the bulk of their funding came from the California Department of Mental Hygiene for the first and federal grants for the second.

Four of us, research psychiatrists, benefited substantially from the construction of the new buildings: Frederic Worden, Arnold Scheibel, Henry Lesse, and myself. The first two were to help me immensely with my academic and research careers at UCLA. Back in 1961, having become a member of the two departments, Psychiatry and Anatomy, and both institutes, NPI and BRI, the new buildings (I still have space in both), signified for me, a beginner in all relevant fields, a huge opportunity that I was ready to seize with zest. In the near future it signified an office in the NPI and a new monkey lab in the BRI.

The rabbit lab in T-67 was doomed anyway for another reason: the VA fire marshal came one day for a visit and, after declaring the building a "fire trap," issued a preliminary eviction notice in advance of demolition. Since the BRI was not yet completed, the four of us UCLA "anatomists" with active projects in that place conferred to decide on the best delaying tactics to hold on to our labs until the BRI was available. I seem to remember that somebody remarked that the form from the fire marshal was printed in 1936, and someone else declared that the VA bureaucracy moved very slowly. We decided to stay put and watchful. A technician pinned a sign on the door of the vivarium: "SMITHY, if you see the wrecking ball coming, (1) pay all your debts, (2) let the animals loose on the field, and (3) run the hell out of here!" Two years later, when I came back from Germany, the building was still there and Smithy in hock.

Munich Max-Planck

Under the generous terms of the NIMH Career Investigator grant, the investigator was allowed to leave the home institution for a 1-year stay in another institution for advanced training. For me, that other institution was to be the Max-Planck Institute for Psychiatry in Munich. There I would join Otto Creutzfeldt in his new department of neurophysiology. Before leaving the States, however, I ensured my return. Then I found out that under the terms of a recent law, a foreign visiting scientist like me was required to spend 2 years abroad before being eligible to reenter the United States as an immigrant. The law was the response of the Eisenhower administration to the pleas by foreign governments to stem their brain drain to the United States. Fortunately, the law did not bar me from spending that

time in other than my native Spain. The NIMH agreed to the extension of my allowed scholarly sojourn from 1 to 2 years, and the University to maintain for me both employment and research facilities during that time.

The Max-Planck Institut für Psychiatrie was a famous historical institution. Situated in Schwabing (in the Kraepelinstrasse, 2), a northern suburb of Munich, it had been built in 1928 to house the research institute founded by Kraepelin in 1917 and to accommodate the scientific facilities of the Nervenklinik of the University of Munich. A long series of prestigious luminaries of the nervous system and psychiatry had worked there: Alzheimer, Nissl, Brodmann, Bumke, among others. After the war, the institute had become one of the Max-Plancks.

When I arrived there, in the fall of 1962, Creutzfeldt was launching a visual neurophysiology program on cats and rabbits. I joined his group, which comprised Dieter Lux, Albert Herz, and Max Straschill, in a series of studies of the visual system designed to clarify the information processing characteristics of its neurons and their susceptibility to changes in arousal level. For me, it was an ideal setting for further training and for pursuing my interests. In cats, we probed the major stations of visual processing: the optic tract (retinal ganglion-cell axons), the lateral geniculate body, and the striate cortex. Two kinds of measurements were our major dependent variables in the three structures: spike frequency and interspike intervals (ISIs). The observations were made under three conditions: spontaneous unit discharge at rest, unit response to brief or sustained visual stimuli, and manipulation of arousal level pharmacologically.

On average, spontaneous discharge slowed down as we ascended the visual system with our microelectrodes. Units fired the fastest in the optic nerve, slower in the geniculate, and slower yet in striate cortex (Fuster et al., 1965a). Those units showed brisk optic responses in the optic tract and weak in striate cortex, with the geniculate cells somewhere in between. In other words, as we went up the visual system, the cells seemed progressively less responsive to external stimuli, and possibly required more specific stimulation in terms of the visual features that we were not testing. The most relevant finding (Herz et al., 1964) was the pervasive presence of interspike interval (ISI) distributions that in the normal resting state approached randomness (Poisson with a minimum interval and exponential decay). Brief visual stimuli induced sharp increases of firing frequency, within which the ISIs still conformed to random—Poisson—distribution but with shorter average intervals. Sleep and drowsiness, whether natural or drug induced, led to phasic activity and reactivity, with ISI distributions containing several modes and prolongation of average intervals. These findings were in accord with the general proposition that in sensory systems information processing is accomplished by changes in neuronal firing frequency, not by changes in spike pattern (that is, by nonrandomly firing units).

In the visual system of rabbits we were able to obtain, for the first time, intracellular records from brain neurons in the wake state or light anesthesia (Fuster et al., 1965b). That allowed us to characterize membrane potentials in those neurons at rest as well as in response to visual stimuli. We showed, also for the first time, that the magnitude of light-evoked membrane potentials (excitatory EPSPs as well as inhibitory IPSPs), in relation to light intensity, conformed well to a logarithmic function, and better yet to a power function. Thus, Stevens' psychophysical power function appeared to describe reasonably well that relationship in visual-neuron synaptic potentials of the rabbit—though the exponent of the function differed somewhat from that observed in human psychophysical experiments.

Back to UCLA: "Limbic Arousal" in Perception

An immigrant with permanent resident status, with wife and two children, I came back to the States in October of 1964. All was well at UCLA. Art Uyeda had taken good care of the monkey lab and was completing the tachistoscopic project. With the new buildings constructed, that lab was now moved to the BRI and my office to the NPI. The rabbits in T-67 were to enter a new study, this one on limbic influences on the visual system.

In the mid-1950s, before he moved to Michigan and later Caltech, the Chicagoan psychologist James Olds stirred considerable interest at UCLA—where he spent 2 years—with his self-stimulation phenomenon: He had discovered (Olds and Milner, 1954) that rats liked to press switches to deliver, through implanted electrodes, current into their limbic structures, notably the hypothalamus and the amygdala. Olds and his group liked to talk about "pleasure centers" in those structures. Among the psychologists interested in self-stimulation were Professor Seward and his graduate student Art Uyeda, who did his thesis research on the reward value of self-stimulation using behaviorist methods. It was Art, later still working with me, who got interested in possible inputs from limbic structures into sensory systems. The issue made a lot of sense to us for two reasons in particular: (a) it is an undisputable fact that emotions alter perception, and (b) there was at that time growing evidence that some limbic structures, especially the amygdala, were involved in the evaluation of the motivational significance of sensory stimuli. Art was to help me strengthen that evidence in the monkey. But first, I wanted to approach the question of "limbic arousal" in a more affordable species than the monkey.

Together with Germán Sierra-Marcuño, a young visiting professor from the University of Santiago de Compostela (Spain), we endeavored to investigate in the rabbit the effects of electrical stimulation of limbic locations on the amplitude of visual evoked potentials (Sierra and Fuster, 1968). The most remarkable finding was an augmentation of the secondary—late—potentials in primary visual cortex by electrical stimulation of the amygdala.

These were the same potentials enhanced by stimulation of the reticular formation of the brain stem. Assuming that the effect reflected increased visual attention, it made sense that input from the amygdala, presumably related to motivation, should increase the cortical manifestation of visual attention.

Also with Sierra we explored in cats and rabbits the psychophysical function of visual potentials: amplitude as a function of light intensity (Fuster and Sierra, 1968). Here again, as in our microelectrode study at the Max-Planck, we found visual response related to light intensity by a power function. The exponent (steepness of curve), however, was quite low, in both lateral geniculate and visual cortex.

In the 1960s, little was known about the behavioral physiology of the amygdala in the monkey other than the effects of lesions of that limbic structure. Most striking among those effects was the so-called Klüver-Bucy syndrome (Klüver and Bucy, 1938), the peculiar behavior of animals that had undergone ablation of the temporal lobe, including the amydgdala in its core. Such animals appeared deprived of emotional feeling, hypersexual, and hyperphagic, prone to eat nonedible objects indiscriminately. From that, it was commonly assumed that the amygdala played a role in the biological value of objects and stimuli. We should expect, we thought, that the neurons in the normal amygdala would react to sensory stimuli that connoted some kind of biological motive. Here is where Art's help would be decisive, among other things because of his strong interest to run limbic experiments on issues of reward and motivation. And now we had the means to drive microelectrodes into deep structures like the amygdala in behaving animals.

We trained monkeys to discriminate between visual stimuli associated with appetitive and aversive consequences: To the monkey, four rows of parallel horizontal lights meant (preceded) food reward; four columns of parallel vertical lights meant (preceded) irregularly a mild electric shock to the feet. Concomitant recording revealed the validity of our prediction. We found cells responsive to the visual stimuli in the amygdala, the hippocampus, and the piriform cortex. Cells responding differentially to the stimuli ("food" vs. "shock") were particularly common in the amydgada. Indeed, in the basolateral amygdala many cells seemed attuned to the motivational significance of the stimuli (Fuster and Uyeda, 1971). In later years, the motivational role of the amygdala would become a big subject among researchers of emotional response in rodents and in human imaging. To my regret, few now cite our work with Art Uyeda (deceased), surely the first demonstration of the involvement of limbic units in emotional behavior. Happily, Joe LeDoux is one of those few.

Psychoanalysis

Another of the intellectual perks of the Career Investigator Award under the National Institute of Mental Health was the payment of tuition for

psychoanalytic training. There were several socio-cultural-scientific reasons for this. In the early 1960s psychoanalysis permeated the zeitgeist of academia, Hollywood, and the press. It was considered a central part of the medical and psychological armamentarium to treat mental illness. It was also a lucrative profession practiced in and out of medical schools by an elite corps of European exiles, some of them disciples of Freud. Because most chairmanships in U.S. departments of psychiatry were psychoanalysts, many of them made psychoanalytic training de rigueur in the postgraduate education of psychiatrists. Besides and behind it all was a deep-seated desire on the part of the psychiatric community to legitimize psychoanalysis as a scientific discipline, thus defeating Popper's dictum that it could never be such a discipline because it cannot be proven wrong.

Logically, psychoanalytic scholars were looking at brain scientists for help. It was against that background that NIMH decided it would be a good idea to train brain scientists in psychoanalysis. Coming from European psychiatric schools, however, where psychoanalysis never really caught on (my own father was decidedly a biological psychiatrist), I did not think much of that discipline. At the same time, I was fascinated with psychiatric phenomenology and with the writings of Karl Jaspers, though not so much by those of Sigmund Freud, who could also be considered a phenomenologist. In time, however, I began to see the intellectual merit in undergoing psychoanalytic training myself.

Thus, given the intellectual and financial opportunity I had (psychoanalytic training was very expensive), I presented myself to the Los Angeles Institute for Psychoanalysis, in Beverly Hills. I told its director, the late Ralph Greenson, that I wished to be admitted to his Institute. Of course, he would not grant my desire without prior scrutiny and consultation. He asked me right away for my motives. I told him that I was genuinely interested in that approach to the human mind. Besides, as a psychiatrist slated some day to train psychiatric residents at UCLA, I could not do without the lingua franca (not my term to him) of psychiatric discourse in my institution. Finally, I told him that, though I was a monkey neurophysiologist, I was truly hoping to find brain correlates of psychoanalytic constructs, and if in the process I found some personal psychic benefit, so much the better. I was not planning to become a full-fledged practicing psychoanalyst.

A few days later, Greenson invited me to his office. The Institute had admitted me for 3 years of formal training. Its admissions board had assigning to me, as personal analyst, one of the very best of their faculty, Hanna Fenichel, the widow of Otto Fenichel, himself Freud's disciple who had written a classic on obsessive neurosis. Perhaps in that connection, the good-humored Greenson asked me, "as one condition for admission," to which I agreed, that one day I would come back to the Institute and reveal to its members the location of the superego in the brain.

Unquestionably, they delivered on their part of the bargain, and I learned a lot I did not know about myself (though some friends claimed it did not do me any apparent good). I did not deliver on my part of the bargain, however, though sometimes I think the superego cannot be too far from the frontal lobe.

The Frontal Lobe

In all honesty, my research on the frontal lobe, which was to practically fill my scientific life for at least four decades, had a scientifically dubious origin. It grew out of a technical achievement, not of the need to resolve a particular research problem—though it ended up doing just that, and more than one. With the help of Larry Ott, an engineer at Hughes Aircraft, I developed thermoelectric cooling probes that could be implanted on the cortical surface of monkeys to induce reversible inactivation or depression of the subjacent cortex. Thermoelectric pairs were then being used by NASA to cool down electronic parts with a tendency to heat up when operating in outer space. I suppose my probes were an example of the much-touted spin-off of space technology into biomedical research. They operated on the Peltier principle, that is, the temperature gradient created by passing electrical (DC) current through adjacent dissimilar metals. If we applied the cold side over the cortex and dissipated the heat at the other side into the atmosphere or running water, we could in effect establish a heat pump to cool the cortex.

Reversible lesions: wonderful! That would put in our hands the functional knockout power of ablation without its imponderable but very real drawbacks, such as secondary degeneration of cells and fibers away from the ablation site, irritation around the edges of the lesion, surrogate takeover of the abolished function by other structures, and so on. More than anything else, the cortical cooling not only would obviate those problems but also would afford the ultimate desideratum for the behavioral neuropsychologist: the ability to use an animal repeatedly as its own normal control. To be sure, as we soon found out, there were limitations to cooling also: sharp temperature gradients in the brain away from the probe, protracted inhibition after the cooling, and the danger of permanent lesion if temperature accidentally reached 0°C. These were some of the reasons why eventually we rarely cooled cortex below 10°C (controlled by subdural thermistors). At that temperature, cortical function could hardly be blocked but simply depressed. That would be useful enough.

In the entire neuropsychological literature on animal cognition, the deficit that monkeys show in short-term memory after frontal ablations is far and away the most consistent and predictable of all experimental deficits (Jacobsen, 1935). Is it a wonder that we should focus on it to test our cooling method? The advantage of reversibility could not be dismissed. Besides, the lateral cortex of the frontal lobe was readily accessible to our cooling probes.

It seemed that we should be able to turn that cortex "off and on" and, thus, short-term memory "off and on." Traditionally, before anyone was concerned with the brain mechanisms of memory consolidation, the delayed-response task and its variants were the time-honored tools to test short-term memory in the primate. And the delay-task deficit from frontal lesion was for many years almost Exhibit #1 of Physiological Psychology 101.

With time, of course, the operational definition of short-term memory by delay-task performance, and the unique frontal-lobe involvement in it, appeared increasingly simplistic. That kind of "operant," "online," "provisional," or "temporary" short-term memory was eventually identified by cognitive psychologists as "working memory," and the frontal lobe was subdivided into a variety of "modules" for functions other than, and in addition to, working memory. But at that time, in the late 1960s, the tempting opportunity to test frontal cooling on such a pristine task as delayed response was irresistible. Again, the experiment was not undertaken to test the validity of the classical finding of Jacobsen, but to test the usefulness of a functional cryogenic method for the behavioral neurophysiology of the monkey. For me, however, it turned out to be my entry into the mysteries of the frontal lobe. It opened my interest into that brain structure that is not the causal source, but certainly the cerebral *enabler*, of such lofty human faculties as language, creativity, and liberty.

At first, the issue was the role of the lateral prefrontal cortex in memory. With my first graduate student, Gary Alexander, we implanted a few monkeys with cooling probes on the frontal lobes and set out to test, this time reversibly, the Jacobsen effect. The result was nothing short of astonishing (Fuster and Alexander, 1970). The bilateral lowering of frontal temperature to 25°C—after all, no lower than ambient temperature—produced a consistent and reversible deficit in the classical delayed-response task. Under cooling, the monkey showed no overt sign of sensory or motor deficit and could perform the task without any problem if the delay, that is, the memory period, was short. When we prolonged the delay to 5 s or more, however, the monkey made more errors of performance than at normal temperature; and the deficit increased with the length of the delay.

Indeed, frontal cryogenic depression seemed to make the animals forget the cue or memorandum, which in that task was a spatial one. The lateral prefrontal cortex was clearly implicated in some kind of short-term memory. Later, with Dick Bauer, a postdoctoral psychologist from Montana, we proved that the dorsolateral prefrontal deficit from cooling could be obtained on a nonspatial (delayed matching-to-sample) as well as on the typical spatial delayed-response task (Bauer and Fuster, 1976). In due time, with Germán Sierra, Jr. we would show a prefrontal cooling deficit on auditory delayed response (Sierra-Paredes and Fuster, 2002).

It took some time before cognitive scientists experimenting with humans, notably Baddeley, in the 1980s would identify as "working memory" the

kind of short-term memory tested by delay tasks in our monkeys (Baddeley, 1983). The capital difference between working memory and the short-term memory that is conventionally considered the gateway to long-term memory before consolidation, is that the former is memory utilized *for a prospective action*. This attribute is the reason why the prefrontal ("executive") cortex is so important for it.

An Interlude with Woodpeckers

One day the late Phil May, a fellow psychiatrist in the UCLA faculty, came to me and blurted out a strange question: "Joaquín, why don't woodpeckers have headaches?" For a moment I was taken aback, but knowing Phil's British sense of humor and sharp intellect, I quickly regained my footing and after some laughter began to appreciate the seriousness of the question. "Phil, I don't know, but I'm sure they don't have headaches; otherwise they wouldn't do all that hammering. It should be fun to find out how their brain is protected from all the shaking and smacking." Then and there began one of the most fun projects of my research career: to study the structure and mechanical properties of the woodpecker's brain and cranial vault.

Our first hurdle was funding, as usual. Everybody in the university found our inquiry amusing, original, and worthwhile, but there appeared to be no local resources for it. Federal money was a possibility. But then Congressman Dingell was already having his own fun scrutinizing government grants for trivial research. Furthermore, there was a protected-species issue. A letter of intent directed to the Navy to solicit help—to go on a Navy ship to Nicaragua in search of specimens—was summarily dismissed, presumably on the suspicion of boondoggle.

Eventually, we found a local source of specimens. Dr. Howell, a senior professor of zoology at UCLA, had a few woodpeckers in formalin that he was willing to donate for our project. A histology lab lent its services for a small recharge. On the whole, the overhead cost turned out to be quite modest and we decided to conduct most of the research on weekends. The results were remarkable in many respects. Before entering the skull of the little critter, we found the most bizarre structure of a tongue, the long thin muscular appendix by which the bird explores the depth of the boreholes it drills in trees searching for tiny insects. The tongue was inserted in the bone around the right nostril and wrapped in a dual coil of split branches around the ears; then its two branches rejoined into one that penetrated the floor of the mouth from underneath the jaw, and its extremity was snugly fit inside the mouth along the beak. We learned what some ornithologists had known for a long time, but we didn't. By uncoiling and sliding over the skull, the tongue could be projected forward to an extraordinary length beyond the beak. Clearly the coiling and uncoiling of the tongue was an ingenious marvel of nature: a highly efficient method to store and use the long tongue.

And, upon its contraction, to project it far and fast forward to dig into the wood.

The anatomy of the bird's head had certain features that we thought of enormous mechanical importance for protecting the brain from injury: *(1)* tight "packing," with no empty or fluid-filled spaces of any significance (consultation with a postmaster confirmed that it could not be otherwise for maximum protection of the skull's content from damage); *(2)* spongy bone at the base of the bill, to act on every impact as a shock absorber; *(3)* an internal crest of bone along the skull's midline, between the two hemispheres—that bony crest, together with the bone on both sides of the skull, was to divert the lines of force away from the brain. Those structural features allowed us to speculate on the ideal structure of helmets to protect soldiers or motorists from frontal impact. With it all, we thought we had enough material for publication in a medical journal. Phil picked it: *The Lancet,* the premier medical journal in the United Kingdom. There, appeared our pride and joy, a paper entitled "Woodpeckers and Head Injury" (May et al., 1976). The editor and reviewers had been happy to accept it with minor revision, complete with a picture of a cross-section of the woodpecker's head and a military helmet from the British Infantry in World War I. As can be imagined, our article generated an enormous amount of publicity worldwide. Eric Sevareid, in NBC's Evening News, announced—in jest—the imminent probability that the government would implement new regulations on the making of helmets for motorists based on our findings in the woodpecker.

The dynamic aspects of woodpecker action were as interesting as the morphological ones. Their study, however, demanded high-speed photography and live birds in action. After contacting Walt Disney Studios, who were in possession of considerable footage of woodpecker hammering for their famous character, we decided to go on our own. We did so especially because commercial film clips, taken at 24 frames/s, did not lend themselves easily to digital analysis of the bird's pecking at an impact velocity of 600–700 cm/s and deceleration nearly 1000 g!

Somehow we were addressed to a ranger in Placerita Canyon Park who had a pet woodpecker, uncaged, hammering away on a tree trunk in his office. The rattle of typewriter keys was sufficient to get the little critter pounding vigorously. With the ranger's permission and the help of an expert cameraman, we took lots of high-speed film footage (2000 frames/s). By digital analysis of the film scans, frame by frame, we were able to reconstruct the action in computational terms. The most remarkable finding was that the bird hit the wood by rapid movements of the head, back and forth, with the beak always orthogonal to the surface of the wood, without any head rotation. This linear motion undoubtedly required an exquisite coordination of neck muscles, but it avoided whiplash and protected the brain from the kind of shearing forces that play havoc in the brains of boxers and motorists (May et al., 1979).

Working Memory: Memory Cells

Whereas my colleagues and I had managed to reversibly reproduce and better define the Jacobsen effect on delay tasks, we had made little progress in understanding the precise form of short-term memory disrupted by prefrontal lesion. As I said before, it was the research by cognitive psychologists experimenting on humans that defined it as working memory. In any case, nothing was known about the physiology behind that kind of memory or, for that matter, about the physiology of the prefrontal cortex. Clearly the data from lesions demanded the microelectrode study of that cortical region in animals performing working-memory tasks. To me, the most elementary questions were: What are the neurons of the prefrontal cortex doing while the animal performs one of those tasks? Could they possibly provide any indication that they engage in retaining the memorandum?

In the late 1960s, when I first dropped a microelectrode in the monkey's frontal lobe, I felt like a paratrooper landing at night in no-man's-land, where danger could come from all sides. Indeed, it was intellectually daring to venture with a microelectrode in "that part of the brain, the size of a fist, which nobody knew anything about"—in the words of a prominent neuroscientist of the time with a slight Canadian accent (David Hubel). I admit I was driven by a simplistic hypothesis in the midst of a fog of ignorance.

But then, expectedly, I struck gold—or so it seemed to me—and the hypothesis proved far from silly (Fuster and Alexander, 1971). I will never forget when I found the first cells that acted like "memory cells" (I had them so labeled for myself even before I found them!). Their distinctive feature was the sustained elevated discharge during the delay, the memory period of a delay task, while the animal had to retain the memorandum (Fig. 2.1). In my initial enthusiasm, however, I ignored the possibility that those cells might be encoding things other than the memorandum. In due time, we would learn from our work and that of many others—especially Japanese investigators, such as Niki and Watanabe—that my memory cells could encode other aspects of the task, such as the impending motor response, the expected reward at trial's end, and the context in which the animal performed its task. We would learn with time that those cells I first discovered in prefrontal cortex were component elements of widely distributed cortical networks that encoded all the associated features of the delay task, a given cell attuned to one feature more than to others. I am now persuaded by the available evidence that those cells are indeed memory cells, but the memory they encode in their ensembles is not only the memory of the memorandum but also the memory of all that the animal has associated in the learning the task to test it.

With Gary Alexander (Fuster and Alexander, 1971), we found memory cells also in the nucleus medialis dorsalis of the thalamus, with which the prefrontal cortex is reciprocally and closely connected. This led to the

Fig. 2.1 Firing of a prefrontal cell during five delayed-response trials (test of spatial working memory). A horizontal bar marks the cue—memorandum—period, and an arrow the end of the delay (memory period) and the response of the animal. Note the persistent activation of the cell during working memory. From Fuster and Alexander (1971).

reasonable hypothesis, which became the basis of Gary's dissertation, that the memory cells of the prefrontal cortex, together with those of its thalamic projection nucleus, were part of the same short-term memory system. Based on that assumption, we were able to show that prefrontal cooling, in addition to impairing delayed response, led to a blunting of delay-cell activity in the nucleus, a suggestion of a working memory reverberating "loop" between prefrontal cortex and thalamus (Alexander and Fuster, 1973). As our exploration of cortical working memory expanded, I was to become increasingly convinced of the existence of such loops between prefrontal and other cortices. Gary, later at Hopkins, would empirically proposed similar loops through basal ganglia in motor programming (Alexander et al., 1992).

In the late 1980s, Pat Goldman-Rakic and her colleagues at Yale (Funahashi et al., 1989), after identifying prefrontal memory cells in a visuospatial delay task and performing elegant parametric studies with them, did much to publicly establish working memory as the primary function of memory cells. She was the most persuasive neuroscientist attributing to these cells the function that Baddeley had first described in the human (Baddeley, 1983).

Contributing from the beginning to my interest in the possible existence of working-memory cells in other cortices was the recognition that the memory activity of many prefrontal cells, while attuned to certain memoranda (e.g., right, left, red, green), was not specifically tuned to them nearly as much as it would be expected from sensory cells (Fuster, 1973; Fuster et al., 1982). Some were evidently tuned, regardless of memorandum, to executive and reward-related features of the task that were common to every trial in it (Quintana et al., 1988; Yajeya et al., 1988). It is true that these were especially concentrated in certain prefrontal domains: executive and working-memory cells in lateral cortex, reward cells in orbital cortex (Rosenkilde

et al. 1981). But the apparently weak tuning of lateral prefrontal memory cells to the cue, which changed from trial to trial, led me to reason in this manner: Could it be that the memory of that cue was actually elsewhere, near sensory cortex and perhaps under prefrontal control, whereas prefrontal cells encoded mainly the memory of executive and reward-related features of the task? Given that in our experiments we were using visual memoranda such as colors, an obvious target for our microelectrodes was the inferotemporal (IT) cortex, a part of the posterior association cortex that lesion studies had shown to be important for visual discrimination and memory. Also its cooling, like that of lateral prefrontal cortex, was shown to induce a reversible deficit in visual delayed matching to sample for colors (Fuster et al., 1981), a visual working-memory task. Later, with Wes Ashford, another graduate student of mine (and psychiatric resident), we would substantiate by field-potential recording the inflow of visual information from visual to IT cortex (Ashford and Fuster, 1985).

As predicted, IT cells were much better at "remembering" colors than prefrontal cells (Fuster and Jervey, 1981, 1982). To be sure, the majority of IT cells did not respond to the sample cue in the color memory task, but many of those that did showed color-specific memory activity during the delay (Fig. 2.2). Evidently, these IT memory cells participated in neuronal ensembles, or networks, that received visual input and, at the same time, retained that input for as long as necessary in accord with the rule of the learned task. It did not appear far-fetched that those networks reached the prefrontal cortex, where they connected with executive and reward networks. It was also reasonable to think that, in turn, the prefrontal cortex reciprocated with some kind of top-down control to ensure in IT cortex the maintenance of attention on, or working memory of, the color of the cue or sample.

The soundness of the last couple of inferences was confirmed by cooling IT cortex and recording from prefrontal cortex, and vice versa, in the course of visual memory-task performance. We were able to correlate the predicted deficits in delayed matching to sample, from cooling either cortex, with the diminished memory discharge of cells in the other cortex (Fuster et al., 1985). Beyond that, the implied cortico–cortical interactions contributed to the network paradigm of cortical memory that was beginning to take shape in my mind.

In any case, my discovery of, and research on, memory cells in association cortices were the most stimulating incentives for writing my two books, *The Prefrontal Cortex* (1980) and *Memory in the Cerebral Cortex* (1995). Both these works are attempts to incorporate my novel findings in comprehensive reviews of established knowledge. The first, now in its foutth edition, has become a universal reference on the prefrontal cortex (Fuster, 2008).

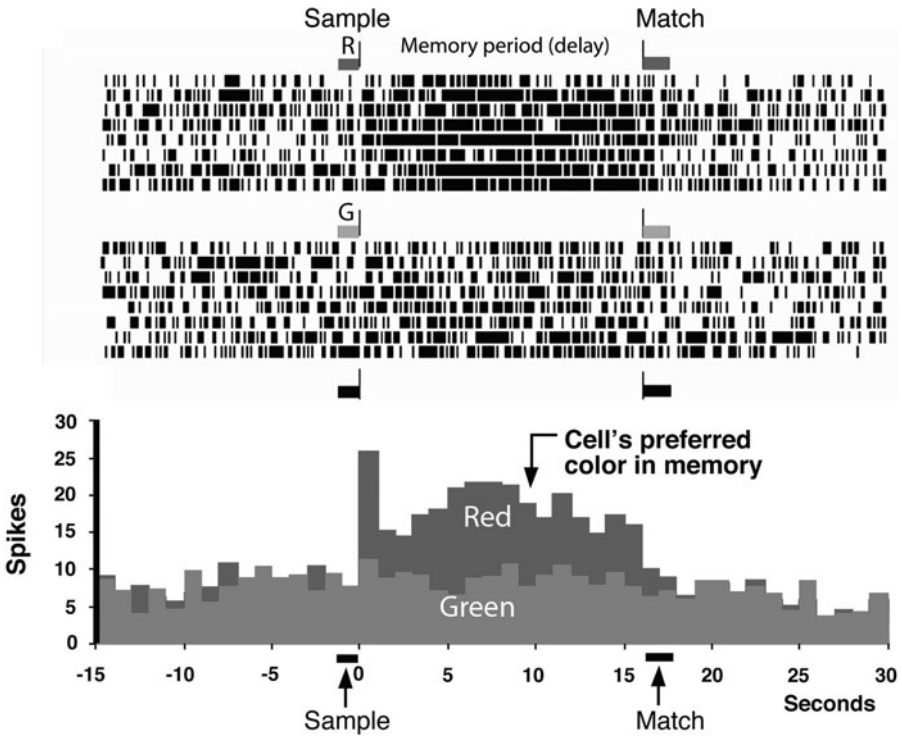

Fig. 2.2 Firing of an inferotemporal (IT) cell during delayed matching-to-sample trials with color (test of visual working memory). The memorandum or sample is a color—red or green—appearing briefly on a central display disk at trial's start. The animal has to retain that color through the delay or memory period, at the end of which the two colors—red and green—appear and the animal has to choose the sample color that started the trial. Though the sample color changes randomly from trial to trial, the cell's activity rasters have been grouped in the upper figure by sample color. R: red sample; G: green sample. The frequency histograms in the lower figure average the cell's firing separately during eight red- and green-sample trials. Note higher cell activity during red memory—and rapid return to baseline discharge despite second foveation of red color for choice (i.e., after working memory is no longer needed). From Fuster and Jervey (1982).

Haptics

In the 1970s and 1980s, the U.S. Navy was very much interested in retrieving the wreckage of the *Titanic* (which Ballard found in 1985 with Navy support). For that and other reasons, the Office of Naval Research (ONR) supported several university research projects bearing on robotics and artificial intelligence. Because at that time I was working with my monkeys

on haptics (active touch or palpation, an essential component of robotics in submarine exploration), they were much more generous to me than they had been for the woodpecker project.

I came into haptics from two avenues. One was my search for memory cells in sensory cortices: haptic memory was as plausible in somatosensory cortex as visual memory was in IT cortex. The other avenue was more theoretical and, as it turned out, closely related to prefrontal function: the idea was growing in me that all cortices serve the broad and basic biological principle of the perception/action (PA) cycle, by which we adapt to the world that surrounds us. In goal-directed behavior, as in spoken dialogue, an external stimulus leads to an action, and that action engenders new stimuli, which in turn lead to new action, and so on. In the dialogue, of course, the environmental stimuli come from the interlocutor. That continuous cybernetic cycling of information through the brain and the environment is the essence of the PA cycle, which governs all goal-directed sequences of behavior, language, and reasoning. Haptic working memory is a means of closing the cycle at the top of the cortical hierarchy (somatosensory/prefrontal), whenever there are temporal discontinuities in the cognition and recognition of tactile information in the course of haptics. Here the "interlocutor" is the physical world of environmental objects.

Eventually, with two undergraduates, Waleed Shindy and Keith Posley, we would be able to show a reversible deficit of haptic working memory by cooling prefrontal cortex (Shindy et al., 1994); cooling parietal cortex would not result in a similar deficit presumably because somatosensory cortex lies mostly in the depth of the central sulcus and out of the reach of our surface-cooling probes. However, with two postgraduates from Spain, Xavier Quintana and Javier Yajeya, we were able to induce changes in prefrontal unit activity in delayed response from cooling the same parietal cortex (Quintana et al., 1989).

All along before and during those cooling experiments, however, we made progress in our exploration of haptic memory in the somatosensory cortex by means of microelectrode recording. Another graduate student, Kevin Koch, found haptic memory cells in that cortex (Koch and Fuster, 1989). The most remarkable finding was that some of those cells were situated in the primary sensory cortex, emphasizing the fact that essentially haptics is a sensory-motor activity, in which the executive and somatosensory aspects of it are inextricable from one another. The microelectrode exploration of that cortex in monkeys discriminating and remembering objects by palpation culminated with my collaboration with graduate student and postdoctoral fellow Yong-Di Zhou, presently director of the Institute for Cognitive Neuroscience in East China University (Shanghai).

Something of general importance came out of my studies with Yong-Di, which was to impact my thinking about the network nature of cortical memory. Whereas John Maunsell (Maunsell et al., 1991) had found units in visual

cortex that responded to the visual *and* tactile features of objects, we found them in tactile cortex (Zhou and Fuster, 1997, 2000). Clearly these cells associated vision with touch. They seemed to belong to broad neuronal networks that reached into visual and somatosensory cortices and associated sensory features cross-modally. We had observed similar cells in prefrontal cortex, these associating the spatial and optic features of visual stimuli used in memory tasks (Fuster et al., 1982), and then later, again in prefrontal cortex, cells that associated sounds with colors in a cross-modal memory task (Fuster et al., 2000).

The supramodal role of prefrontal networks had been previously supported in cross-modal cooling experiments. Having achieved the not easy task of training monkeys to discriminate objects by touch (without cheating as in 5F!) and to perform haptic memory tasks (DiMattia et al., 1990), we had been able to show deficits in these tasks by cooling lateral prefrontal cortex (Shindy et al., 1994). Especially noteworthy for us, in that it reinforced the cross-modal character of the prefrontal cortex, was the evidence of deficits induced by cooling this cortex on visuohaptic and haptic-visual working-memory tasks, where the animal had to memorize an object perceived by touch and recognize it by vision, or vice versa.

A Paradigm Shift in Cortical Memory

The cross-modal effects of prefrontal cooling, and the evidence of cross-modal cells in parietal and temporal cortex, among other findings, were slowly but surely leading me away from the conventional thinking of sensory physiologists about the role of the cortex in perception. Up until practically the end of the century, most of them were heavily influenced by the modular organization of visual cortex. Beyond this cortex, they thought, modules probably got bigger and specialized in ever more complex optic features. In the mind of some, hierarchical complexity meant that in higher cortex there would be some integrative neurons ("grandmother cells") that would put all the sensory features of a percept together. No one really believed in that absurdity, but many endeavored to develop modular models of cognition, more or less parallel and more or less hierarchical, down to the computational and neuronal levels, all of them based on the sensory properties of visual stimuli. None of them, that I knew, dealt with neuronal integration of behaviorally associated stimulus properties.

In the 20th century the word *network* appeared often in the neuroscience literature on cortical cognition, but rarely with formal definition in neuronal terms. "Neural network" was an expression coming from information theory and artificial intelligence that penetrated the field of cognition in multiple attempts to model the dynamic connectivity of brain structures. But the concept of cognitive network (*cognit*, my expression) for representation

of memory and knowledge in the cortex never quite entered cognitive neuroscience. The conspicuous absence of practically any network concept of cognition in the large compendium of *The New Cognitive Neurosciences* by Gazzaniga (2000) prompted my sharp critique of that book (Fuster, 2000), which I am sure did not make me many friends.

Actually, however, the general idea of cortical cognitive network had been proposed long ago by some brain theoreticians with regard to one cognitive function or another (Edelman and Montcastle, 1978; Mesulam, 1981; Bressler, 1995). The first proponent, and undoubtedly the most influential on my thinking, was Hayek, a famous economist (Nobel Prize 1974) who in his youth (1920s), while a student of psychology in Vienna, had written an insightful essay about perception that was to be published much later under the title of *The Sensory Order* (Hayek, 1952). In that essay Hayek prophetically envisioned the network concept of perception. Perception, according to him, consisted of the workings of a memory-constituted apparatus of dispersed but interconnected cortical neurons classifying the world as we sense it on the basis of prior experience. Memory and perception were inseparable in all respects (as Helmholtz had previously held). The key neural structures *for both functions* were assemblies of intersecting memory "maps" with common nodes. These "maps" (his unfortunate word for isomorphic networks without any relation to the well-known retinotopic maps) were formed by associative learning through facilitation of synaptic contacts by temporally coincident input stimuli. Hayek's specific concept of the synaptic basis of learning and memory was akin to one of Hebb's principles (Hebb, 1949). But his original cortical network concept of memory and perception anticipated by many years the use of methods for axon staining, the demonstration of the rich network-like connectivity of the primate cortex, and the identification of fiber tracts by functional imaging.

Four fundamental lines of evidence from our research led me to the conceptualization of a new reticular memory paradigm in the cortex based on Hayek's concepts, a paradigm that at least in my mind was to supersede the modular paradigm that was a commonly held legacy of the 20th century. One line of evidence was the observation that the areas of the primate cortex with working-memory cells of a given sensory modality were, to judge from the effects of their lesion, known to be involved in long-term memory of the same modality. In the human, injuries of their homologous areas cause agnosias, amnesias, and discrimination deficits of the same modality. From there, the idea emerged that working memory is essentially a fragment of long-term memory updated for present usage.

The second line of evidence was that in practically any part of association cortex, including prefrontal, memory cells could be found that were attuned to several stimuli, whatever their modality, that had been associated by the animal in the learning of a working-memory task. What's more,

we had gathered evidence that the learning of a memory task was correlated with increased responsiveness of cells to its associated stimuli. These findings were most striking in our cross-modal memory experiments (Zhou and Fuster, 2000; Fuster et al., 2000; Zhou et al., 2007).

The third line of evidence derived from our study of the cellular mechanisms of working memory. Cell firing patterns in association cortex showed replicates and periodicities that were consistent with the concept of network reverberation as one of those mechanisms (Villa and Fuster, 1993; Zipser et al., 1993; Bodner et al., 1998, 2005; Verduzco-Flores et al., 2009).

The fourth line of evidence came out of our imaging studies. By means of positron emission tomography (PET) with neurologist Barbara Swartz and others, we were able to ascertain the joint cortical activation of large prefrontal and visual areas in humans performing a visual working-memory task (Swartz et al., 1995). Presently, with graduate student Allen Ardestani we are investigating the dynamic coherence in cortical networks of monkeys performing such tasks. We use an integrative methodology that includes the recording of multiple-unit discharge, local field potentials (LFPs), surface field potentials (SFPs), and near-infrared spectroscopy (NIRS). The recording of the last of these signals is a method for assessment of changes in cerebral blood-flow secondary to neuronal activity, a method that is relatively novel for the monkey (Fuster et al., 2005), and possesses high temporal resolution.

In my view, the emerging paradigm of cortical memory, which I first proposed in 1995 (Fuster, 1995; Fuster, 1997) and later in *Cortex and Mind* (Fuster, 2003) is receiving increasing support from the latest findings by innumerable investigations of working memory using the latest techniques of neuroimaging and electrocortical computation. I summarize that support in a recent review article (Fuster, 2009).

Central to the new reticular paradigm of memory is the concept of the *cognit*: a neural unit of knowledge or memory consisting in a cortical network of widely distributed neuronal assemblies. That network is formed, expanded, and modified by learning or experience. The component assemblies may consist of smaller networks representing discrete sensory or motor items of information in sensory or motor cortical modules. Cognits are formed by the temporal coincidence of sensory or motor inputs to those assemblies. In accord with the Hayek-Hebb principle ("cells that fire together wire together"), the representational assemblies or "netlets" concomitantly activated are united by synaptic modulation into larger associative networks that represent the composite of the simultaneous stimuli or inputs. A newly constituted cognit will be thereafter activated in its totality by activation of only one or a few of its component assemblies. Furthermore, two or more components of different cognits, when coinciding in time, will lead to the association of those cognits into higher and more abstract or complex cognits. Those will share common nodes of connectivity and representation.

We have known for a long time, as a result of studies of neuropsychology in patients with temporal-lobe injury (Squire, 1987), that for memory to form and consolidate in the neocortex, the hippocampus and probably other limbic structures need to intervene functionally. The synaptic mechanisms by with this occurs, however, are still poorly understood. Certain excitatory neurotransmitters, such as NMDA, are supposed to play a role in the underlying neural transactions. Whether electrical phenomena such as long-term potentiation also play a role remains a matter of debate. In sum, cognitive networks or cognits vary greatly in size and distribution, some of them straddling noncontinuous areas of the cortex. The cognitive code they represent is essentially a relational code, in which the information is defined exclusively by the relationships between component cognits or assemblies of neurons. It is a code irreducible to its parts, much as the code identifying visual percepts in Gestalt psychology. The idiosyncrasy of our knowledge and memory thus derives from the practically infinite combinatorial power of our 10 to 20 billion cortical neurons. Because of the heavy intersection and overlap of cognitive networks, one neuron or group of neurons practically anywhere in the cortex can be part of many memories or items of knowledge. The cortical networks constituting cognits are hierarchically organized, from the simplest and most concrete in sensory or motor cortices to the most complex and most abstract in the higher association cortices. Perceptual cognits are principally organized in posterior cortex, whereas executive cognits are principally organized in frontal cortex. All cognitive functions (attention, perception, memory, language, and intelligence) are based on neural transactions within and between cognits. There are powerful reciprocal connections between posterior and frontal cortices for the dynamic interactions between the two cognitive hierarchies in the perception/action (PA) cycle, which is the neural substrate for the organization of behavior, language, and inductive reasoning.

Memory of the Future

This is undoubtedly the most awkward oxymoron for the title of the last part of an autobiography. I have two quick explanations for it. First, the expression best characterizes the position of my favorite brain structure, the prefrontal cortex, in evolution and in the temporal organization of adaptive behavior. Secondly, the expression is at the crux of my current interests in the neurobiology of liberty and free will.

Once in 1984, my Swedish friend, the late David Ingvar, asked me to edit an issue of his journal, *Human Neurobiology*, to be dedicated in its entirety to the prefrontal cortex. I undertook my task with a great deal of interest, anticipating his contribution in particular, for he was a pioneer in the neuroimaging of the prefrontal cortex. That contribution did not take long to reach my hands. To my astonishment its title was “Memory of the

Future." I demurred. Indeed, it took me a while before I understood the paper and accepted it, as I eventually did pretty much as it was and with that title (Ingvar, 1985). It turned out that Ingvar had been the first to demonstrate the activation of the human prefrontal cortex during the ideation of plans of action and language. He saw in the human the prospective memory that I was still missing in my monkeys and in their memory cells.

After a couple of decades I have come to appreciate the wisdom of David's expression perhaps even more than he himself did. For, much as in evolution, the prefrontal cortex "invents the future" based on the past. Executive memory is literally memory of action to adapt to the future. Evolution, with the prefrontal cortex in its vanguard, is the manifestation of the PA cycle at the population level. In both the individual organism and the population, that cycle uses the memory of the past to adapt both the organism and the population to their environment. The brain intervenes in the former, the genes in the latter.

Our freedom consists not only in our capacity to choose between alternative actions but also in our capacity to choose between alternative sources of past information to plan and guide those actions. The prefrontal cortex, at the apex of the PA cycle, enables both, the choice of information and the choice of future action. Just as the species carries in its genes the information it has acquired to adapt to its environment, the prefrontal cortex has at its disposal an enormous reservoir of acquired perceptual and executive memory to adapt to that environment. Moreover, in what is a veritable quantum change in evolution, the human brain has acquired two basic and characteristic capabilities, both in large part the purview of the prefrontal cortex: language and the capacity to predict. Both are intimately related with each other and allow us to *preadapt*, not only as individuals but also as a society. Both serve the memory of the future. Societal memory is the root of institutions, laws, and ethics. In all those personal and public endeavors our individual prefrontal cortex is the *supreme enabler*: enabler of what is already in the brain, in the form of either past or prospective memory or imagination. Most certainly, the prefrontal cortex is not the implicit "homuncular CEO" of some current accounts, a conceptual fallacy resulting from modular thinking that inevitably leads to an infinite regress.

Only the future provides meaning to our autobiography. I shall thus close this account of mine with a brief future perspective. Next week, I am supposed to deliver the annual Segerfalk Lecture at the University of Lund, where David Ingvar spent his last professional years. The lecture will be on the frontal lobe; I could not think of a better title for it than "Memory of the Future." To the distant future, Elisabeth, my dear wife of 52 years, and I have made two significant contributions. One is a happy family with three children and six grandchildren. The other is a private legacy to the University of California. In recognition of the unstinting support I have received throughout my scientific career from this great institution, we have

endowed it with a chair in Cognitive Neuroscience. The first holder of the Fuster Chair is Professor Susan Bookheimer, a renowned expert in brain imaging and a superb educator.

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