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Yadin Dudai

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# Yadin Dudai

## **BORN:**

Tel-Aviv, Israel  
December 8, 1944

## **EDUCATION:**

Hebrew University, Jerusalem, Israel, BSc with distinction, Biochemistry, Genetics (1969)  
Weizmann Institute of Science, Rehovot, Israel, PhD, Biophysics (1974)

## **APPOINTMENTS:**

Research Fellow, California Institute of Technology, Pasadena, CA (1974–1976)  
Scientist, Weizmann Institute of Science (1974–1977)  
Senior Scientist, Weizmann Institute of Science (1977–1980)  
Associate Professor, Weizmann Institute of Science (1980–1988)  
Professor, Sara and Michael Sela Chair in Neurobiology, Weizmann Institute (1988–)  
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The J.F. Kennedy Prize, 1974  
The Glucksman Award, 1983  
Fogarty Scholar in Residence, National Institutes of Health, 1991–1995  
Annual Distinguished Lecture, University of Edinburgh  
College of Medicine, 1998  
Public Lecture Series, College de France, Paris, 2002  
D.O. Hebb Lecture, McGill University, 2003  
The Annual Volker-Henn Lecture, University of Zurich, 2005  
The Eduardo de Robertis Lecture, Argentina, 2007  
The Annual Carl P. Duncan Lecture, Northwestern University, 2011  
Honorary Member, Argentinian Society for Neuroscience, 2012  
Fellow, American Association for the Advancement of Science, 2012  
Fellow, Association of Psychological Science (APS), Washington, DC, 2012  
Fondation IPSEN Neuronal Plasticity Prize, 2013  
Member, European Molecular Biology Organization, 2014  
Member, Israel National Academy of Sciences and Humanities, 2014  
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*Yadin Dudai explored neurobiological mechanisms of single-experience memory. He was in the team that discovered the first memory mutants of Drosophila, providing the proof of concept for the molecular neurogenetic analysis of memory. He then discovered that the mutations affected memory rather than encoding and described consolidation and roles of the cAMP cascade in cellular and behavioral plasticity in the fruit fly. He developed a multilevel approach to investigating memory in the behaving rat brain, using conditioned taste aversion as a model, and identified posttranslational modifications in receptors and signal transduction cascades during the encoding and consolidation of memory in the mammalian cortex. He also identified behavioral and brain processes of memory extinction and reconsolidation and their competition over behavioral control, and proposed boundary conditions and models of reconsolidation of long-term memory (including the dominant trace hypothesis and the lingering consolidation hypothesis). He developed protocols for analyzing realistic episodic memory in the human brain and described mnemonic roles of the hippocampus in the first seconds after experiencing an event and in integrating new information, including social influence that distorts memory.*

# Yadin Dudai

**S**tudents of memory are rather suspicious of the veracity of recollections. Yet although flashbulb memories are not spared the distortion of time and use (Christianson 1989), the fact that the recollected rare moment has emotional uniqueness is seldom doubted. Sometime in high school, in the 11th grade (or was it the 12th?), in a biology lesson, the same teacher that so often kicked me out of the class and swore loudly to God that nothing would ever come out of me, caused me to experience a mini-epiphany and start a lifelong love affair with biology.

For more than 50 years I have never reconstructed the details of that event. Only the emotional gist remained. In preparation for this essay, I started a small detective investigation, guided by fragments of reminiscences: it was botany, it was evolution, it was unrelated ends suddenly falling into place to create an unexpected plot. I located an old botany textbook (Harder et al. 1965), bought a new one (Mauseth 2014), followed by still another one on evolution (Willis and McElwain 2014). It was like sailing to an abandoned personal Ithaca. Soon, I reached the conclusion that the flashbulb moment was that in which I realized that a flowering plant hides within itself another, miniature organism; the two protagonists in this story are the same encountered independently much earlier in evolution in green algae, embodying the alternation of haploid and diploid generations typical of plants. Nature has concealed one creature inside the other. This was an amazing nature-made narrative, providing the restless teenager with a startling example of evolution and experience of the sublime. Decades later, was I re-enthralled? Admittedly, less so. First times are difficult to reenact. In the search for the evasive memory, I also was gratified to re-witness how much the life sciences have changed. The older textbook had no molecular biology whatsoever.

The reader who has made it to this point in the essay might be lured into thinking that my journey into science followed naturally. This, however, was not the case. Life had surprises.

## Tel-Aviv, on the Mediterranean

I was born on December 8, 1944, in Tel-Aviv, a bustling city that was expanding rapidly on the sandstones of the Mediterranean beach north of Jaffa. I grew up as the youngest son in a posttraumatic family. My parents' big families were murdered by the Nazis and their collaborators in Lithuania and Poland in 1941–1943. My father, Aharon-Zvi, and my mother, Batya,

immigrated to Palestine shortly before World War II. They never again saw those left behind. Both were from a Lithuanian *shtetl* in which Hebrew culture flourished and the dream of returning to the land of Israel was kindled for generations. Years later, while preparing a family book for my grandchildren, I took a DNA test and realized that the origin of our ancestry is indeed in the eastern Mediterranean basin. And if the shock of the holocaust was not enough, my elder half-brother was killed in Israel's War of Independence. Ongoing bereavement was a fact of life.

My early years were spent in times of war. Unfortunately, wars kept intruding into my life since then. Snipers from Jaffa used to fire on our house. On one occasion bullets landed in my bed, in my absence. I do seem to recall a snapshot of bullet holes in the wall; this recollection does raise questions about childhood amnesia or about reconstructive memories. That war ended, I went to a religiously oriented school, moved to a secular school, and then spent memorable years at a high school in Tel-Aviv. If grades are the criteria, I was far from being a good student, except in composition, and my mother had to come to school quite often to hear from the principal that I was terribly disruptive. I was socially constructive, headed the students' council, contributed to the school newspaper, and organized parties. I was not engaged too much in contemplating the future. Some days, I considered becoming a doctor, but then I watched a movie in which a young physician spends his days pampering newborn bottoms with talc, and my enthusiasm dwindled. Despite my attraction to biology, I was not sure it was a future. I considered seriously, in fact, becoming a professional journalist.

This decision materialized more quickly than expected. During the summer break after the school year I found work as a switchboard operator at the leading Israeli daily, *Yediot Ahronot*, to earn pocket money. This was an old-type switchboard in which the lines had to be connected manually to close the circuit. It was a hot stuffy basement of an old building. All this led me to experience a behavioral paradigm that I was to encounter years later in science: fear conditioning. The unconditioned stimulus was the shock delivered through my sweating fingers each time I closed the circuit. The conditioned stimulus was the ring signifying the request for calls. The number of callers, some mumbling unintelligibly, seemed to be directly proportional to the frequency of shock. Late at night, rats crossed the room, making the situation even worse.

I was rescued by the political cartoonist Ranan Lurie, who wandered downstairs out of curiosity. A short conversation was initiated, I gave an affirmative answer to his question as to whether I could write, and composed a short item (signed "special correspondent") on the health risk of eating overcooked meat (about which I had read somewhere before; Polish food was always overcooked). This piece was published and attracted the attention of the omnipotent editor, Dov Yudkovsky, who transferred me to the news desk, where I found myself converting boring texts written by confused

correspondents into terse statements and catchy titles. Soon I found myself arriving at the news desk daily before dawn, struggling with the racing clock to crank out headlines as part of a small team of editors all of whom were much older than me. The disciplinary experience of those predawn routines served me well in later years. Yudkovsky, the editor whom everybody feared, also appointed me as his personal assistant, exposing me at that early age to the political and social intricacies of Israel. Many years later, he invited me to say a few words at a public ceremony honoring him on the occasion of his 80th birthday. I thanked him for his role in my life. He started his speech by thanking me for not accepting his advice to pursue a career in journalism. Traces of his childhood dreams to gain a formal education, shattered in the extermination camps in which he had strived to survive as a lonely child, surfaced in his speech.

## Wars, Peace, and in Between

Being young in my class, I was given the opportunity to enroll for a year in Tel-Aviv University immediately after graduating from high school and before the compulsory service in the Israeli Army. In parallel to gaining experience in journalism, I studied philosophy and history. When the time finally came, the army decided that my experience would be of some use as a combat correspondent. I became the chief combat correspondent of the army weekly magazine. Given the lack of electronic media, that magazine was in fact the major communication channel of the army and often the government. This meant, on the one hand, joining units in the field and becoming embedded in commando raids across enemy lines, and on the other, spending time with the high command and sometimes with the prime minister. Looking back, I think that those years endowed me with some sense of proportion, traces of a capacity to distinguish the critical from the less so, and a better appreciation of the complexity of human behavior. It also made me get rid of any fear of authority. This went well with my innate *chutzpah*. Furthermore, witnessing intimate moments in the life of a nation imprinted me strongly on my homeland.

Toward the end of my army service, I was summoned to the office of the chief of the intelligence services. He offered me an immediate short-cut to a special officer course, promising a fast career track. This was one of the toughest decisions of my life. After a sleepless night, I declined. I felt I needed a more systematic education, and that it should be done now, before falling into the muddy pond of international affairs, or never. I also declined offers from newspapers. The inherent superficiality of journalism was always in the back of my mind. Over the years, I did remain occasionally engaged in state and in public affairs. These chapters are not covered here.

In one of the last months of my army service, while in a jeep approaching the gate of an army base, the driver and I noticed two girls in military

uniform attempting to hitchhike to the closest city. We stopped. One of them was Rina Hon. About a year later, we married and she has been my partner ever since. Her wisdom and loving influence cannot be overstated. Some good things do come out of the army. Rina and I were already together when I had to leave on an army-related mission to Europe only to return shortly before the Six-Day War, in which I participated, as did other Israelis of my generation.

I then found my way back into the university and this time decided to give biology a try. I graduated with distinction from the Hebrew University in Jerusalem, majoring in biochemistry and genetics, with supplements in modern history. My attraction to the humanities kept kicking in. In fact, the first job offer I ever got in academia was to serve as research assistant in modern history. I was kicked out of the room of the history department chair when I said that I couldn't accommodate the itinerary because it conflicted with my biochemistry lab assignments.

At that time, Rina and I moved to Jerusalem, and already had our daughter, Orit. Our son, Rani, was born a few years later, after another fierce war, the Yom Kippur War, which I barely survived.

## Weizmann Institute of Science: The Tale of an Enzyme with a Tail

It was my experience in journalism that brought me to the Weizmann Institute of Science. While a student at the Hebrew University, I supplemented our income by working as an editor in a Hebrew popular science magazine, whose editorial offices were conveniently located in Jerusalem. The chief scientific advisor of that magazine was a professor of biochemistry at the Weizmann Institute, Nathan Sharon. Sharon asked me about my plans, I replied that they included MSc studies in genetics at the Hebrew University, and he commented that although this option would be brilliant, he would still arrange for me to visit the Weizmann Institute and meet with Professor Ephraim Katchalski (Katzir), chair of the Department of Biophysics. I had heard beforehand about the excellence of the Weizmann Institute, and knew who Katzir was, but the real-life encounter made a strong impression. The milieu was more research oriented than at the Hebrew University, and Katzir greeted me as though I was already in. He told me that he was usually quite busy and suggested that although he would still be officially in the picture, I should select a younger faculty to mentor me in the lab. He introduced me to Israel Silman, just back from his postdoc training in the United States. Following that visit, I decided to join the Weizmann Institute. Silman (known as Sili to his friends), a brilliant biochemist, spoke fast and wrote in miniscule indistinguishable ink specks, and the first expertise I had to acquire in the lab was to understand what he really wanted.



I took several courses in physical chemistry, including advanced math, statistical thermodynamics, and quantum physics, to ensure that I had the proper quantitative background. I have hardly used these subjects since, but am grateful to the teaching committee of the Feinberg Graduate School of the Weizmann Institute for making me take these courses. Among others, they have proven to be an effective long-term preventive medicine against intimidation by talks in computational neuroscience. As to the lab, we decided that I would join a long-term project concerning the structure and function of the nicotinic acetylcholine receptor from the electric organ of the electric eel. Because another student, Nurit Kalderon, was doing exploratory experiments along these lines, we thought that I should first engage in an interim project that was supposed to take a few weeks only: purification of the enzyme acetylcholinesterase (AChE) from that same tissue, with the goal of later crystalizing it. The major role of this enzyme, one of the fastest in nature, is to hydrolyze the neurotransmitter acetylcholine, which plays a critical role in the neuromuscular junction and the brain. AChE is the target of many poisons, including nerve gases and insecticides, as well as, more recently, drugs to alleviate symptoms of the early stages of dementia.

What was supposed to be an interim project took years and became my thesis topic, later to be pursued by generations of students in Silman's lab. We thought it was a short-term project because a report in the literature claimed to have already purified and crystalized the enzyme. This report may have been premature. Furthermore, little was known at that time about the biochemistry of the cell membrane, let alone about the integration of enzymes and receptors into the membrane. I therefore embarked on a new approach, affinity chromatography. One of the founding fathers of this method, Professor Meir Wilchek, was down the corridor. The idea was to couple an enzyme or receptor inhibitor to an insoluble resin, apply to the conjugated resin a preparation such as a tissue homogenate containing the target protein, wash to elute the molecules that are not retarded by the inhibitor, and then elute the target protein specifically with a soluble inhibitor. We coupled inhibitors of AChE to a resin, applied homogenates prepared from the electric organ tissue, washed out the unrelated proteins, and then eluted the enzyme specifically by applying a solution containing another powerful AChE inhibitor. As with many things in science, God is in the details: I had to struggle for months to find the right conditions. At first, we were able to purify an AChE form that sedimented as an 11S particle on a sucrose gradient, present in a proteolytic digest of the homogenate (Kalderon et al. 1970, Dudai and Silman 1971, Dudai et al. 1972a). We then moved on to a stronger inhibitor and were able to purify on the affinity column heavier, native, nondigested forms of the enzyme, of 14S and 18S size (Dudai et al. 1972b). I proceeded to further separate the enzyme forms by sucrose gradients, and then subjected them to analysis in an



analytical ultracentrifuge (to determine the molecular weight) and the electron microscope (to determine the shape; Dudai et al. 1973). The molecular weights ranged from about 335KD (11S) to 750KD (14S) and 1100KD (18S). They seemed therefore to represent multiples of a basic entity.

The surprise came with the electron micrographs of the heavier, native forms of the enzyme. They unveiled a head, consisting of a large number of subunits, and an elongated tail; the 11S was a tetramer devoid of a tail. This finding was so unexpected that I first thought I had purified some miniphage contaminant, and I was in fact later relieved when I learned that similar structures were observed in parallel in the laboratory of a French colleague. This was the first time that I encountered the Janus face of competition in science. On the one hand, it kindles the anxiety associated with the primitive drive to win the race. On the other, traces of stoicism can convert it into a reassuring reward if it confirms one's own findings. These findings opened a new era in the study of AChE; the tail was later proven to be of a collagenous nature and served to anchor the enzyme in the synaptic cleft. In the decades since then, the study of AChE from various sources has flourished tremendously (Dvir et al. 2010), but one thing remains: it is still a tale of an enzyme with a tail.

The surprising findings concerning AChE compensated for hard and often boring work. I keep telling my students that the ability to withstand delayed gratification is essential for a scientific career. This conclusion came from those long weeks of boredom washing columns in cold rooms or in front of the giant analytical ultracentrifuge. I also discovered that I am not a one-method person, and am happy to learn any method that fits my ongoing goal and abandon that method equally happily when it doesn't fit anymore. My later career proved that I am also not a single-experimental preparation person. The questions and concepts seem to excite me more.

Silman was a great mentor. Wise, stimulating, highly knowledgeable, always available to listen and help, and, on top of it all, open minded. And as for Katzir, we in fact worked together a lot and became quite close, but this had little to do with my thesis. He was extensively involved in state affairs and schlepped me in. He was elected the president of the State of Israel in 1973 and requested that I serve as a special assistant to the president on some matters. I found myself spending many hours, often on short notice, at the president's office in Jerusalem. My life adjusted literally to a 24/7 schedule.

In the meantime, as I was contemplating my future, my department chair, Professor Uri Littauer, arranged for the president of the Weizmann Institute, the physicist Professor Israel Dostrovsky (the father of Jonathan Dostrovsky from the now classic O'Keefe and Dostrovsky 1971), to offer me a position before I left. Dostrovsky had one condition, I should never go into politics. He previously had served as head of the Israeli Atomic Energy



**Fig. 1.** Tough decisions. The J.F. Kennedy award ceremony at the Weizmann Institute, toward the end of my PhD thesis, with Prime Minister Yitzhak Rabin (shaking hands), and Professor Israel Dostrovsky, then the president of the Weizmann Institute (to his right). Becoming immersed early in life in professional journalism and in a hectic compulsory army service, rendered early career decisions somewhat more difficult. The conflicting advice I got didn't make it easier. For example, Rabin, whom I came to know in the army, told me shortly before he became the prime minister that in his view the "university of real life" is much more interesting than life in academia (on his second term as prime minister, however, he became an avid supporter of science and technology at large). Probably sensing my hesitation, Dostrovsky made the offer that I join the Weizmann faculty contingent on my promise that I never would go into politics.

Commission, and his extensive interaction with politicians conditioned him to spare me the experience. This was an easy promise to keep.

### Caltech: A *dunce* Is Born

I first saw Seymour Benzer when he gave a talk at the Weizmann Institute on the neurogenetic dissection of behavior in the fruit fly, *Drosophila melanogaster*. I came out of the talk somewhat disappointed because the speaker presented no mechanisms. To a young biophysicist and biochemist, this was blasphemy. It took time for the ingenuity of Benzer's approach to dawn on me. In the months thereafter, in a mostly implicit process, I realized that here is a minimalist, boldly reductionist approach to complex problems. Though fresh in neuroscience, this was the same approach that led to smashing success in the dissection of genetics and metabolic pathways in lower organisms. Benzer's brilliant studies on the dissection of the RII locus in the bacteriophage T4 were breakthroughs in our understanding of the structure and function of the gene and have become classic textbook material (Benzer 1962).

During that period, I was still engrossed in an incessant internal discourse on whether I really wished to commit myself to a lifelong scientific

career. I enjoyed the action, milieu, and intellectual adventures, but also missed the bustling life outside the bubble. I ultimately made a decision: I would apply for a single postdoctoral position only, and if not accepted, would reevaluate whether the scientific commitment indeed fitted me. Benzer's approach looked more and more appealing and a bit mysterious. I thought that one could apply it to an enticing problem, namely, identifying genes that make people smarter. The possibility cannot be excluded that this was an urge implicitly kindled in me during my earlier nonscientific careers. In any event, I wrote Benzer a letter, stating my wish to join his lab and work on smart mutants. Within a few weeks (remember, no Internet yet), a reply arrived. Benzer said that I probably understand that it is much easier to find stupid rather than smart individuals, and furthermore, work on learning and memory in *Drosophila* and a search for stupid mutants already had begun in his group by Chip (William) Quinn. If I wished to join this effort, I should request two scientists to write letters of recommendation. I reached the conclusion that looking for stupid mutants is not a bad starting point, and asked Silman and Katzir to send the letters. Shortly afterward, the logo of the California Institute of Technology (Caltech) reigned again on the corner of the almost transparent airmail envelope waiting for me in the departmental mail box. The response said, "I have now received the letter from Professor Katchalski-Katzir and have learned that he was elected the president of the State of Israel, so you should keep his signature because it will be worth lots of money. However, would you please send me a letter from somebody who really knows what you are doing?"

I cherished this no-nonsense reply, asked for another letter of recommendation, and shortly afterward was invited to join the Benzer lab. The door to the unique world of fly genetics in Caltech was now open. But life, again, had its surprises. A terrible war erupted in October 1973, and my departure suddenly appeared to be an unrealistic dream. Benzer was considerate enough to write that my position was secured and that this should be the least of my worries at those difficult times. I switched from thinking about science to thinking about survival, found myself in some unbelievable situations, and unfortunately, as with almost all my colleagues, lost friends to the cruelty of war.

I was able to join Benzer's group in Caltech in October 1974. A few weeks before that I participated in the fly course in Cold Spring Harbor and acquired some basic skills in fly work. My encounters with coursemates and the teaching staff were encouraging and heartwarming, and these were a harbinger of the impressions and esprit de corps that I was to later encounter in the fly community. I arrived in Pasadena alone, assisted by the hospitality of Danny Michaelson—at that time, a postdoc with Mike Raftery and later to become an expert on Alzheimer in Tel-Aviv University and a lifelong friend—and waited for my family to join. I then became immersed in fly neurogenetics and behavior. Letters from Katzir kept arriving from time to

time, alerting me to the fact that the situation in the Middle East was much less favorable than in the fly world.

I consider Caltech to be my true scientific alma mater. Although I spent less than two years there, its scientific influence could not be overstated. Much has been written about Benzer and his fly group (e.g., Dudai 2008). The place epitomized the way I thought science should be conducted—that is, with originality, seriousness, drive, and persistence, yet without losing sparks of modesty, and engulfed with collegiality and joie de vivre. On the one hand, we mastered every trick of fly genetics and behavior, and on the other, we could spend hours stuffing flies into an empty orange just to be able to release them in class to make undergrads remember forever their first encounter with the fruit fly. Caltech also encouraged development of bullshit detectors, a useful mental device that unfortunately is not used sufficiently in current public relations-driven scientific culture. Nobody claimed they made breakthroughs daily, although some did achieve many. Max Delbruck, Ed Lewis, Richard Feynman, and other scientific legends were around, expressing keen interest and, from time to time, volunteering idiosyncratic advice on science and life. Daily lunch meetings were a mix of discussions of the latest restaurant experience along with recent advances, or setbacks, in our projects. So different from some current attempts to convert neuroscience into corporate-culture science.

When I arrived, Quinn already had left and Duncan Byers was engaged in the memory mutant search in his kind, thoughtful, melancholic manner. Quinn had developed the first successful memory assay of *Drosophila*, based on olfactory avoidance or fear conditioning. The assay worked well only on fly populations, whereas memory conventionally was expected to be tested in individuals; in *Drosophila*, however, this was not a problem, because we could breed fly populations in which individuals were genetically identical. Stampede effects notwithstanding, we could heuristically consider the behavioral test of a population of 40 flies as an approximation of 40 tests of a single fly. The idea was to mutate flies under conditions that result in only one to a few mutations per chromosome and to take advantage of the fact that a normal male carries only one X chromosome. Therefore, iso-X fly progeny will display single-mutational events on the X. Mutagenesis was done by feeding flies with ethyl methanesulfonate. The progeny populations were then each subjected to memory tests on the fear-conditioning paradigm, which we kept improving.

Looking back, this was a daring, risky project: we were able to generate and test only a few hundreds lines in the course of a year, and each line had to be tested several times to allow sufficient statistical power to deem that a mutational event indeed impairs behavioral plasticity. One of my scientific grandfathers, Professor David Nchmansohn from Columbia University who pioneered research on the biochemistry of the cholinergic synapse, once told me that science depends on three Gs: *geduld*, *geld*, and *gluck* (German for patience, money, and luck). Although I didn't completely



**Fig. 2.** Happy discoveries. Celebrating *dunce*, the first *Drosophila* memory mutant, in Caltech. From left to right, upper row: Yuh-Nung Jan, the author, Chip Quinn, Bill Harris; bottom row: Duncan Byers, *dunce*, Seymour Benzer. Years later, upon seeing this picture, some noted that this might have been not only the proof of concept of neurogenetics of memory but also of the effectiveness of trans-species reverse genetics.

agree with him—imagination and a pinch of anarchy were missing from the list—*gluck* we surely had. Mutant lines 38 and 276 repeatedly were showing signs of stupidity. By that time, I was already practically navigating the pace of the team project, spending days in small darkened rooms testing one fly line after another for memory and carrying out control tests for sensory-motor thresholds on candidate dumb flies.

The single-gene neurogenetic dissection approach was not without its loud adversaries, among them classic population geneticists, who favored multiple trait selection and achieved only little in elucidating mechanisms, and behavioral biologists, some of whom doubted the ability of *Drosophila* to learn at all. One day somebody brought to the lab the front page of a local newspaper, stating that “Flies are stupid but dolphins use sonar.” Benzer was more affected by the opposition than we were, and uncharacteristically needed our explicit support. Maybe he felt confident in molecular genetics but less so in behavior. Another day, a television team came to the lab to produce a movie on fly behavior. The heat from their lamp killed the fly they filmed, but for them it didn’t make a difference.

The putative mutant lines were both defective in performance on the conditioning test despite displaying otherwise-normal sensorimotor behavior. We proceeded on the first line, and after convincing ourselves that we had something real, dubbed it *dunce* (*dnc*; Dudai et al. 1976), aptly commemorating the 16th-century theologian John Duns Scotus, whose followers were ridiculed by contemporary humanists as enemies of learning. The other

line was also a *dnc* allele. I characterized the behavior of these and other lines of flies, including many existing mutants (Dudai 1977). We tried in parallel to get some hints on potential biochemical defects in the mutants, using pharmacology. Together with Yuh-Nung Jan, we discovered that feeding wild-type flies caffeine, a cyclic-AMP phosphodiesterase (cAMP PDE) inhibitor, makes them *dunce*-like. This was merely a hint, however. Direct evidence that *dunce* was a mutation in an isoform of cAMP-PDE came only later in the collaborative work of Byers, Ron Davis, and John Kiger (Byers et al. 1981). Interestingly, mutations in the same gene were identified in three different screens: for learning deficits, for female sterility, and for activity of the cAMP cascade. In fact, line 38 (*dnc<sup>1</sup>*) reduced the fecundity of females to about 50 percent and line 276 (*dnc<sup>2</sup>*) to only 2 percent. Clearly, although the mutations had a relatively specific effect on behavioral plasticity, they also affected other biological processes. But we were looking for clues about the mechanisms of memory, and here they were.

At about the same time, I also found that *Drosophila* memory consolidates—that is, it undergoes a transient maturation process after which it becomes resistant to amnesic agents. This was important because it showed that the memory we are dealing with is similar in a basic property to memory described in mammals. The trick was to identify the proper nontoxic amnesic agent that could work fast and reproducibly. It was cooling. Placing the flies briefly in a plastic tube in an ice bucket was sufficient to anesthetize them, and recovery was rapid as well. This was a clear Caltech influence: look for the simplest solution. Cooling immediately after training, but not a few minutes later, erased subsequent memory—a clear proof of consolidation. What happened when I shared my finding in the daily lunch meeting was typical of the Benzer lab. Benzer reacted softly: this is an important finding. Quinn (then in Princeton) just shared with me this morning that he found the same thing. Why don't you both get on the phone and publish together? I flew to Princeton, we coauthored a note to *Nature*, the only manuscript in my career that was accepted without even a single comment from the editor (Quinn and Dudai 1976). No scoopophobia (Dudai 2002a) in the small fly community those days.

## Starting My Own Lab at the Weizmann Institute

Both Benzer and I agreed that although it would be fun to continue, I had achieved my planned goals and the time had come for me to start my own lab. It was also time for Rina, who studied literature at UCLA, to return to her work and studies in Israel. Two years away from home, as much as we enjoyed them, seemed enough to us. We hence returned to Rehovot, not before stopping on the way for two months in Utrecht, Holland, for me to gain experience in rat neuroanatomy, neurohormones, and behavior in the Rudolf Magnus Institute of Pharmacology, under the guidance of Professor David



de Wied and with the generous help of Willem Gispen. I wanted to keep my future options open and familiarize myself with the most common memory model in neurobiology those days. This indeed came in handy years later.

I established the first *Drosophila* lab at the Weizmann and proceeded to analyze in fine detail the behavior of the learning mutants (Dudai 1979, 1983), to investigate receptors and their signal transduction cascades in the fly brain, and to identify their contribution to behavior and behavioral plasticity (Dudai and Zvi 1982, 1984a, 1984b; Uzzan and Dudai 1982). I should note that at first it was not easy to convince my colleagues at Weizmann that flies are real animals, and as a back up, I hired a PhD student to do some rat neuroreceptor work so that we could walk down the corridor with rat cages to show that we were also serious scientists. (That project triggered in fact a set of informative studies on the role of neurotransmitter receptors in the brain of the rat; e.g., Ben-Barak and Dudai 1979, 1980.) I remember that on one international site visit an eminent biochemist from the West Coast came to my lab and upon seeing the milk bottles with the fruit flies jumping inside, asked why I wasn't waiting for them to grow bigger. The research on *Drosophila*, however, soon provided intriguing results and the attitude of the milieu changed. First, I discovered that *dnc*, and another mutation isolated in the laboratory of Quinn, *rutabaga* (*rut*), are in fact memory mutants and not learning mutants: they perform reasonably well in the memory test immediately after training, but their memory decays rapidly (Dudai 1983). This was important, because, together with our earlier findings on memory consolidation, it showed that the memory can be dissected into subprocesses, rendering it more likely that specific mutations will affect different memory processes and thus allow mechanistic dissection of the memory machinery step by step. Second, we found that *rut* is also mutated in a component of the cAMP cascade, this time in a subtype of the enzyme that generates cAMP, adenylyl cyclase (Dudai et al. 1983, 1985; Dudai and Zvi 1984a, 1984b, 1985). Quinn's lab also reported that *rut* is defective in adenylyl cyclase (Livingstone et al. 1984). Third, we described the biochemistry of multiple components of the cAMP cascade in wild-type and mutant *Drosophila* and their role in behavior (Buxbaum and Dudai 1987, 1988, 1989a; Orgad et al. 1989), and a data-driven kinetic model was proposed to explain how persistent activation of a component in this cascade, the cAMP-dependent protein kinase, may subserve long-term plasticity (Buxbaum 1989b). This model fit the concept that memory could be encoded by molecular switches based on the operation of protein kinases (Crick 1984; Lisman 1994).

The implication of the cAMP cascade in *Drosophila* memory also triggered a collaboration (and a long-term friendship) with Eric Kandel and Jimmy Schwartz at Columbia University, the shrine of *Aplysia* memory. I spent a sabbatical there in 1982, which also was used to familiarize myself with new developments in molecular biology, with the kind advice of Richard

Scheller and Tom Maniatis, across the street from the Kandel and Schwartz labs. To convert theory into skill, I took part in cloning the *Aplysia* calmodulin gene. Kandel and I and our teams became particularly interested in the role of the  $\text{Ca}^{2+}$ /calmodulin-sensitive form of adenylyl cyclase ( $\text{Ca}^{2+}$ /CaMAC) as a coincidence detector that subserves stimuli associations in conditioning (Eliot et al. 1989; Yovell et al. 1992). I was particularly intrigued at that time by the possibility of identifying properties of  $\text{Ca}^{2+}$ /CaMAC that might explain elementary operations of biological learning machines (Dudai 1985).

The question underlying this interest is fundamental to this day: can behavioral properties be inferred from molecular properties? A tenet of the reductionist approach is that molecular and cellular properties can explain systems and behavioral properties (for an opposite view, that higher, more global levels are agnostic to the inner working of lower levels, see Laughlin and Pines 2000). For example, those who advocate long-term potentiation (LTP) as a cellular device of memory argue that LTP subserves memory not only because in some cases LTP has been shown to correlate or interact with memory performance, but also because the cellular model shows properties similar to those of memory, such as associativity and persistence (Dudai 2002a). In this case, we specifically wanted to test whether the properties of  $\text{Ca}^{2+}$ /CaMAC can account for properties of memory performance. Our idea was that the enzyme is a coincidence detector on which the molecular representation of the conditioned stimulus (CS) and the unconditioned stimulus (US) converge. On the basis of findings from the gill and siphon withdrawal reflex in *Aplysia*, in our model,  $\text{Ca}^{2+}$  was considered to be the cellular representation of the CS, and the transmitter serotonin was considered to be the cellular representation of the US. Classical conditioning is successful when the CS starts before the US. We therefore hypothesized that optimal activation of the enzyme requires  $\text{Ca}^{2+}$  to precede serotonin by a fraction of a second. Together with my student Yoram Yovell and with Tom Abrams, we built what then was considered to be the ultimate reductionist dream machine: an apparatus for a continuous assay of  $\text{Ca}^{2+}$ /CaMAC in response to transient pulses of  $\text{Ca}^{2+}$  and transmitter (Yovell et al. 1987). We used this system to quantify in detail the kinetics of  $\text{Ca}^{2+}$ /CaMAC and its interaction with key cellular cations, and the potential relevance to plasticity (Yovell et al. 1987, 1992). This system was later used to show that in *Aplysia*  $\text{Ca}^{2+}$ /CaMAC peak activation occurs when  $\text{Ca}^{2+}$  precedes the transmitter pulse (Yovell and Abrams 1992).

Two caveats are noteworthy, however. First, many macromolecular entities, ranging from receptors and channels to transcription factors and promoters, can be considered to be coincidence detectors (Dudai 2002a). If  $\text{Ca}^{2+}$ /CaMAC indeed implements a basic property of biological memory machines, it is only a single token in the type of molecular devices that the nervous system uses to embody temporal associations in behavioral and developmental plasticity. Second, even more important, should one expect

the properties of a molecule to mimic the properties of behavior, or, in other words, the properties of the whole to be identical to the properties of one or more of its components? This, in fact, is not remote from the homunculus fallacy (Dudai 2002a): the belief that a diminutive system resembles the bigger system in which it resides and reads information and commands action within that bigger system. This is not a satisfactory explanation because it is a slippery slope to the assumption of homunculi (or turtles) all the way down. These issues prompted me to pay increasing attention to the distinction between neuronal plasticity and memory, which the contemporary molecular and cellular literature sometimes blurred. I will return to this fundamental distinction in the following. In the meantime, suffice it to say that in my internal mental discourse, I considered the molecular underpinnings of neuronal plasticity as the elementary nuts and bolts that permit and constrain the encoding of information in the higher system level and, as such, indeed can display some basic properties that also are expressed at the higher level, whereas memory is the specific content embodied in and expressed by the higher level and therefore cannot be reduced to molecular devices. The study of neuronal plasticity therefore is not identical with the study of memory and is not expected to unveil homunculi that have the same knowledge as their intelligent host.

Conceptual unrest notwithstanding, all in all, the experimental work in the fruit fly did proceed nicely (Dudai 1988). However, even in our successful neuronal plasticity playground, we did not identify a dihydromemorase or data-convertase. Rather, we identified gene products that are variants of molecular building blocks used by nature for many processes, including elementary neuronal function and development, and furthermore, that are not necessarily exclusive to the nervous system. The conclusion was in line with the idea, consonant with aforementioned remarks, that to account for specificity of information, one must consider how neurons are interconnected, and hence the study of memory should involve an identification of the circuits that subserve a specific behavior. This was easier said than done. The *Aplysia* people did achieve this, but they lacked the powerful tools of genetics, and this is what the *Drosophila* community was still missing in those early days. The methods available were not yet suitable for dissecting identified circuits in the central nervous system of the fly. I am not a method-oriented person and furthermore the resources available to me at that time did not make the development of novel imaging and physiology techniques a realistic goal. Initial attempts to convince a colleague, whose expertise was imaging, to devote some energy to development of methods in *Drosophila* were unproductive.

The solution we found, together with my student Gabriel Corfas, was to turn to the peripheral nervous system. We thought that if the work on *Aplysia* was so successful in dissecting a sensory-to-motor reflex, why shouldn't we try to follow the same line of thought in the behaving fly. We

developed for that purpose a “cleaning reflex” paradigm, based on the observation that upon tactile stimulation of its thoracic bristles, the fly cleans, with a patterned set of leg movements, the field covered by the stimulated bristles. We found that this reflex can undergo habituation and dishabituation. Single sensory neurons that mediate the input and the output and motor neurons that mediate the behavioral output are identifiable. Therefore, the system is useful for exploring the effects of single-gene mutations on behavioral and developmental plasticity in a prewired system. Most promising, we found that a memory mutant showed abnormally short-lived habituation.

Gabriel was able to record from the mechanosensory neuron and identify sensory adaptation and fatigue as physiological correlates of the behavior. Both *dnc* and *rut* altered the kinetics of the sensory fatigue. This was the first time that the effect of memory mutations was identified on the functional properties of an identified neuron that subserves a modifiable behavior in *Drosophila*. The results also indicated that the memory mutations affect fundamental neuronal plasticity properties and that the relation between the molecular defects and memory would not be straightforward: whereas both *dnc* and *rut* impaired classical conditioning in what seemed to be a similar way, they displayed opposite effects on sensory fatigue. We also found that the fine morphology of the identified mechanosensory neuron is abnormal in both *dnc* and *rut*, with an abnormally large number of side branches and varicosities, which were identified as potential synaptic sites. This showed that the mutations in the cAMP cascade play a role in shaping neuronal connectivity and link behavioral and developmental plasticity (Corfas and Dudai 1989, 1990a, 1990b, 1991).

This preparation probably could have sufficed to nourish scribomania from our lab until retirement. But the big question (what is the proper way to tackle the machinery of memory?) kept bothering me. Does a peripheral neuron in the fly satisfy my urge to understand memory? Again, do I make the proper distinction between neuronal plasticity and memory? What is the way to identify the correspondence rules between the two, assuming that indeed neuronal plasticity is the engine of behaviorally expressed memory?

At about the same time, I reached another conclusion, known probably to many, that the most powerful (and admittedly painful) way to master a field and reassess one’s own knowledge, worldview, and aims is to write a book on the topic. I also realized that despite the availability of excellent books on memory, none, to the best of my knowledge, provided a multi-level integration of the contemporary neurobiology of memory. The result was *The Neurobiology of Memory. Concepts, Findings, Trends* (Dudai 1989). This monograph was not only an integrative précis of the field as I saw it but also a statement: if you study only molecules or synapses or even neurons in isolation, you are bound to study plasticity. Memory is about a change in specific behaviorally related content embodied in activity states

and patterns of in situ systems; it is about the change occurring with experience in internal representations, that is, models of the world encoded and computed in neuronal space. Plasticity mechanisms modify (or preserve) the representations, but the content is provided by the circuit functioning in the specific neuronal context in the behaving brain. Hence, my conclusion: go to the brain, young man.

But which brain? It is of note that the methodology for studying the fly brain was at that time much less developed than that required for exploring the mammalian brain. I had to make the decision on whether I next devote years to the development and compilation of the suitable methodologies, and I decided against it. I felt that I might for years distance myself from the study of memory per se and likely would end up with a description of a modifiable reflex, which is great but less to my personal liking. I also felt that it was about time to start dealing with a brain that is more similar to our own. Flies are beautiful, but they think and speak flyish. Even Benzer used to say that he studies the fly brain only to model the human brain, although at a later stage, he commented that after acquiring more experience with people, he reached the conclusion that the human brain is a model for the fly brain.

## On Béarnaise Sauce and Rats

At that time, most of the knowledge on the biological underpinnings of human memory still was based on pathology, inferring function from dysfunction; noninvasive methods with a reasonable spatiotemporal resolution to study a healthy brain were lacking. I wanted to work on a normal brain. I was not personally comfortable with working on primates (I did travel to NIMH, to Mort Mishkin's lab, to get the flavor), not to mention that molecular tools, which were one of my entry points, were practically a no-go in primates. This restricted the choice to rodents. My engagement in the study of *Drosophila* had led me from the outset to focus on the encoding and consolidation of information acquired in one-shot experiences in naturalistic conditions. I was looking for a system that could allow me to pursue this line of investigation.

One candidate stood out: conditioned taste aversion (CTA; Garcia et al. 1968, Bures et al. 1998). This is the learned association of taste with visceral distress. Farmers know well that animals tend to avoid poisonous bait if they survive their first encounter with it. Humans are more familiar with the version in which consumption of spoiled falafel or Béarnaise sauce induces long-lasting specific avoidance of the foodstuff (this is why CTA is also dubbed the Béarnaise sauce effect). Amazingly, a phenomenon considered as obvious by the layperson was rejected for years by editors of scientific journals, because it didn't fit all the rules expected from conventional classical conditioning (efficient associativity of diverse types of stimuli, brief interstimulus interval; Garcia 1977). CTA was easy to achieve in the rat by

pairing a novel taste solution with subsequent transient malaise induced by intraperitoneal injection of lithium chloride. Quite a lot was learned over the years on the behavioral phenomenon and on some brain correlates (Bures et al. 1998). Mechanistic analysis, targeting identified brain areas with molecular and cellular tools, was lacking, however. Furthermore, from reading the literature, it became clear that a neocortical area (in the insular cortex) was suspected to be involved. Taken together, this appeared as a suitable candidate for multilevel integrative dissection of the mechanisms of learning and memory in the mammalian cortex. We could benefit from much previous knowledge on the one hand, but add novel approaches and a fresh mechanistic view on the other.

Before long, along with my students Kobi Rosenblum and Noam Meiri, we showed that the insular cortex not only is involved but also is a major site of consolidation of both the taste memory and its associative trace (Rosenblum et al. 1993). This finding paved the road to work conducted over several years during which time we identified behavioral and brain mechanisms of memory formation and storage of taste and CTA, focusing on the insular cortex and in some experiments on the amygdala. This effort involved many in our group (e.g., Lamprecht et al. 1995, 1997; Rosenblum et al. 1995, 1996, 1997; Lamprecht and Dudai 1996; Naor and Dudai 1996; Berman et al. 1998, 2000, 2003; Berman and Dudai 2001; Bahar et al. 2003, 2004a, 2004b; Desmedt et al. 2003; Eisenberg et al. 2003; Guitton and Dudai 2004; Kobilio et al. 2007; Shema et al. 2007, 2009, 2011; Guitton et al. 2008). Overall, we combined behavioral analysis, biochemistry and molecular biology, pharmacology, neuroanatomy, and some electrophysiology. This is not a review of the field, yet a few findings are worth noting *en passant*. Among them are the following discoveries: (1) the tyrosine phosphorylation of the 2B subunit of the *N*-methyl-D-aspartate receptor (NR2B) is involved in initiating memory in neocortex; (2) the mitogen-activated protein kinases (MAPs) ERK1/2, and their downstream substrate ELK1 are instrumental in downstream signaling in memory formation; (3) the stimulus-induced transcription factor cAMP response element-binding protein (CREB), previously identified to play a key role in neuronal plasticity in invertebrates, plays a similar role in the mammalian brain; (4) the molecular and circuit mechanisms of learning a new item are different from those of learning new things about a familiar item; (5) encoding of novelty of an item requires a cholinergic signal in cortex; and (6) memory extinction, that is, learning that an association is not relevant any more, is not a unitary processes, but rather the sum total of multiple processes, some of which conflict with each other in their effect on behavior. This, by the way, was a conclusion I reached over the years: whenever you detect a behavioral phenomenon, analysis will expose richer subprocesses, sometimes competing with each other, and these subprocesses can be used to manipulate the outcome of the system (another example is noted in the following section).



In the earlier *Drosophila* days, we were toying with the idea of using genetics to enhance memory. Soon after we described the role of tyrosine phosphorylation of NR2B in neocortical memory in the behaving rat, Joe Tsien, then at Stanford, reported a transgenic mouse overexpressing NR2B with enhanced learning and memory (Tang et al. 1999). This achievement resulted, as expected, not only in a high-profile publication but also in catchy headlines in the lay press. Enters pleiotropy: again, as with the fly mutants, the effect on memory was not on memory only—in this case, unfortunately, it was accompanied by a decreased threshold for pain (Wei et al. 2001). This echoed not only Benzer's skepticism concerning the ability of neurogenetics to increase wisdom but also a moral committed to my memory during religious elementary school: "he that increaseth knowledge increaseth sorrow" (Ecclesiastes 18:1). In Hebrew, it sounds even better, as "sorrow" in the original is in fact "pain." Whether this is a universal maxim is still for science to find out, but the possibility that we may pay a dear price if we ever seriously attempt to genetically enhance our species' biological memory should be kept in mind.

Many of these findings identified nuts and bolts of memory consolidation, that is, the transformation of the trace over time from an early, malleable form, to a mature, more firm form (Dudai 1996, 2002b, 2004, 2012; Dudai and Morris 2000). My interest in consolidation goes back to the *Drosophila* days. Note, however, that despite my long-term investment, I never discarded the possibility that consolidation is not a "natural kind" (Quine 1970), but rather it is a convenient way to classify a set of phenomena because it makes it easier for us to construe what we think the brain does with the learned information. The question of natural vs. anthropo-created types kept occupying me throughout my career, and will resurface below. Furthermore, in its original form, the consolidation hypothesis presumed that it occurs just once per memory item, but much evidence has accumulated that this is not the case and that items in long-term memory (LTM) can "reconsolidate" after their reactivation.

"Reconsolidation" was first proposed in the 1960s (Misanin 1968), subsequently practically muted by the zeitgeist (Sara 2000), and then boldly revitalized by Nader (Nader et al. 2000). Our work on the consolidation and later extinction of CTA fed into the debate and provided some insights. We were able to dissociate brain mechanisms that contribute to consolidation and reconsolidation (Bahar et al. 2004a). Most notably, we found that in memory retrieval, among the multiple associations invoked by the available cues, the association that comes to control (dominate) behavior is paradoxically the one that becomes more sensitive to interference in the hypothetical process of reconsolidation, which results in diminishing subsequent memory (Eisenberg et al. 2003). I was particularly gratified to learn that Joe LeDoux, a leader in memory research who is also a gifted musician, wrote a song about our dominant trace model for his rock band, The Amygdaloids ([http://www.amygdaloids.com/?page\\_id=463](http://www.amygdaloids.com/?page_id=463)); only that in the song, the

dominant trace is never erased, in real life it is. Another type of collaborative work with another dear friend, Richard Morris, on spatial memory in the rat, led to the conclusion that for reconsolidation to take place at all, something new must be present in the retrieval situation, so that an encoding state is engaged (Morris et al. 2006).

These and additional findings (e.g., Eisenberg and Dudai 2004) led us to conclude that as opposed to synaptic or cellular consolidation, which is universal and reported in every system and paradigm of LTM, reconsolidation takes place only under certain boundary conditions. One of these is the strength of the trace (“dominant traces” tend to reconsolidate); another is the need for something new to appear in the retrieval situation (“encoding mode”); still another is probably the age of the memory (old memories tend to reconsolidate less). It became evident that reconsolidation, extinction, and memory updating all interact with each other, raising again the issue of the natural kind. For the brain, all these phenomena may reflect a continuum of computations, sometimes competing, performed in the postactivation state (Dudai 2007). These findings also have resulted in the hypothesis that what we identify as reconsolidation is in fact an additional phase in consolidation, that itself consolidates (the lingering consolidation hypothesis, see Dudai and Eisenberg 2004). The idea was that a major function of consolidation is to form retrieval links rather than reinforce the core representation itself and that this consolidation lingers much longer than previously thought.

A common method to identify consolidation is to use agents that block memory only within a limited time window after encoding. But what happens if an agent is found to block memory long after consolidation is assumed to be over? This is what happened with the zeta inhibitory peptide (ZIP), the pseudosubstrate of the enzyme protein kinase M zeta (PKM $\zeta$ ), a member of the family of protein kinase C proteins. Following the findings of Todd Sacktor on the ability of ZIP to erase LTP and memory in the rat hippocampus (Pastalkova 2006), we found that ZIP blocks long, even very long (several months), CTA memory in the neocortex, which is considered the ultimate repository of many types of memory in the mammalian brain (Shema et al. 2007, 2009). These results were astonishing, as this was the first case of an agent that specifically could erase consolidated memory in the absence of the need to reactivate the memory (i.e., not by blocking reconsolidation). This was taken to suggest that the activity of PKM $\zeta$  is critical in maintaining LTM. Being quite experienced in enzyme biochemistry, however, the use of an inhibitor to conclude that the assumed target is involved appeared somewhat risky. Therefore, we used genetics and discovered that overexpression of PKM $\zeta$  enhances LTM performance long after encoding, whereas overexpression of a dominant negative form of the gene blocks LTM (Shema et al. 2011). The former result was particularly intriguing: how could an “old” memory be enhanced by an enzyme? The jury is out on the role of PKM $\zeta$  in maintenance of LTM (Sacktor and Fenton 2012;

Volk et al. 2013). As these lines are being written, we are struggling in our lab, together with our colleague Menahem Segal, to understand what ZIP really is doing at the cellular level, and we have some doubts as to whether its amazing effects on memory are a consequence, or only a consequence, of the inhibition of PKM $\zeta$  (Sadeh et al. 2015). Having said that, studies from several labs continue to indicate a role for PKM $\zeta$  in memory (Hardt et al. 2013; Xue et al. 2015). Stories in science are never as simple as they may look at a first glance, and this only renders them even more interesting.

In the meantime, upon entering mammalian brain projects, my research group has largely diversified. The background of my students and postdocs now ranged from psychology to molecular biology and computer sciences. This diversity also reflects the general increasing interest of smart students in the brain sciences. I realized that for them to interact efficiently, furthermore to navigate in the field more productively, they needed to become more familiar with basic notions and concepts about memory and to learn to speak a common language. I embarked on what turned out to be the most demanding and difficult project that I have ever done: write a book that defines, gives the historical and conceptual framework, and discusses more than 130 keywords and concepts that I wished my students to know (Dudai 2002a). In fact, this was akin to writing more than 130 books. The entries ranged from *a priori* to *zeitgeist*, with representation of multiple levels of analyses and subdisciplines. There were extra terms related to the culture of science, *scoopophobia* being but one example.

The investigation of reconsolidation, extinction, or use-dependent updating of memory raises fundamental questions concerning the relevance of memory to reality. If the trace metamorphoses with use, what is the relevance of the expressed representation to the original event? These issues naturally are better studied in humans. Furthermore, functional imaging methods had been developed that rendered the noninvasive study of the human brain more accessible. The opportunity for me to use these methods came soon.

## Human Correct and Erroneous Recollections

In 2004, the Center for Neural Science at New York University offered me a position as Global Distinguished Professor of Neural Science (later to become the Albert and Blanche Willner Family Global Distinguished Professor of Neural Science). This post allowed me to become integrated in the research and academic life of the outstanding New York University (NYU) neuroscience community, yet still retain my position at the Weizmann Institute and avoid the need to relocate from Israel. Since then NYU has become my second home, and I am grateful to my colleagues there for their friendship, wisdom, insight, and support, particularly to Joe LeDoux and Tony Movshon. NYU has a cutting-edge center for human brain imaging and memory, and it is there that I was trained in human fMRI and in the adaptation of human



**Fig. 3.** Cross-level integration. My interest in cross-level translation of concepts, processes and mechanisms of memory in general and of the encoding and consolidation of one-shot real-life experiences in particular, was a driving force in gradually shifting my lab from studying the fly brain to exploring the human brain. In a recent version of my research team, only one student is still using molecular biology in the rat brain, whereas the others combine their training in psychology, biology, neuroimaging, and computer science to study the encoding and time- and use-dependent transformation of human episodic memory. From left to right, standing, are Micah Edelson, Noa Sadeh, Ella Bar, Noga Cohen, Meytar Zemer, the author, Uri Korisky, Neetai Eshel; and seated are Catarina Raposo (a student in another group, adopted by us given that she married Micah), Maya Shemesh, Aya Ben-Yakov, and Liat Pell.

memory protocols to the scanner. In parallel, at the Weizmann, while still pursuing at full speed our work on single-shot learning in the rat neocortex, I started to develop memory protocols to quantify episodic memory in humans under naturalistic conditions. The human episodic memory literature was remarkably rich and deep, but much of the work had been conducted along the Ebbinghausian tradition of using artificial stimuli and associations. I wanted to go into real-life memory, as I firmly believe that the brain, that of humans as well as that of other species, operates differently in natural contexts than when facing artificial and often admittedly boring stimuli.

The idea was to use narrative movies to simulate episodic experience. Movies are amenable for use as stimuli in the scanner, and they can be tailored in content and length to the requirement of different encoding and retrieval situations. Movies have been used by Uri Hasson at Weizmann to study visual perception and develop novel fMRI analysis methods. Because we wanted our participants to be able to face novel situations in a natural context, one of the first actions we took was to produce movies of our own. A team in our lab, with the assistance of a few cinema studies students, produced many hours of documentaries, centering on the life of an Israeli student. On top of the fun, the advantage was that the movies were filmed in Hebrew, and whereas commercial movies avoid boring the viewer, we

wanted to achieve the opposite, to mimic the style of most real-life routine situations. The first movie that we used in the scanner, however, was a rather tedious episode from an English-speaking sitcom unlikely to have been seen by students and more suitable to be used at NYU because of the language and the context.

We started sailing into the marvelous world of human episodic memory (Tulving 1983; Squire et al. 2004), amazed to discover how well participants remember incidental, useless events, and realizing the important role of social information (and its brain underpinnings) in encoding realistic episodic memory. Analysis of the behavioral and brain mechanisms of the formation and the transformation of episodic memory started in collaboration with colleagues at NYU (Furman et al. 2007; Hasson et al. 2008) and proceeded in parallel as well as independently in Rehovot (Mendelsohn et al. 2009, 2010). We found that the episodic trace is transformed over weeks and months into a semantic form, in which the neocortex supports context-poor recollections in the absence of significant hippocampal involvement; however, if context-rich, vivid recollections still surface even after months, they still are associated with hippocampal activity. The role of hippocampus in storing LTM is hence task dependent (Dudai 2012). Furthermore, we found that over weeks and months, the brain shifts into a parsimonious neural mode in recollecting the event, leading us to suggest that metabolic frugality was a driving force in shaping systems consolidation (Furman et al. 2012).

Selected elements of the rich behavioral repertoire of humans was translated in our work into a set of encoding, consolidation, and reconsolidation projects, including another collaboration with NYU, on encoding and memory following insight, which by definition, is a one-shot task (Ludmer et al. 2011). Some of the projects were clearly unconventional. We used hypnosis in the scanner to identify brain circuits that inhibit the expression of episodic traces (Mendelsohn et al. 2008). We also used a large live snake to create a paradigm for rapid switching between fear and courage in the scanner to identify rapid alternations in dominant traces in retrieval (see trace dominance earlier and Nili et al. 2010). Work in the lab was really fun, with those still pursuing memory in the rat brain enjoying the movies created by their peers studying memory in the human brain.

## Personal Memory, and That of the Other

In recent years, my work has shifted increasingly to focus on behavioral and brain mechanisms of the consolidation of human episodic memory. Much of the more recent work has been devoted to two topics. The first topic of interest examined the first seconds of realistic episodic memory and the triggering of consolidation (Ben-Yakov and Dudai 2011; Ben-Yakov et al. 2013, 2014; see also review in Cohen et al. 2015). In other words, what happens in the brain in the “big bang” of memory, those first seconds that influence

the fate of memory in the years thereafter? Here, using brief movie clips as memoranda, we discovered that the hippocampus seems to wait for a few seconds, possibly until the episode makes sense, before initiating consolidation. We also found memory-related involvement of the striatum in these critical seconds, a region so far mostly considered as supporting nondeclarative memory. Indeed, this brings up again the issue of natural kinds: we are used to classifying memory into declarative and nondeclarative, yet it is unclear whether those are natural kinds in the brain, or whether the brain recruits computational modules as the situation demands without necessarily honoring our taxonomy. We also found a way to dissociate the contribution of the hippocampus to encoding and retrieval in a single experience, because in real life, even novel experiences have familiar elements, and hence rarely, if at all, do we encode without retrieving at the same time. Again, two competing computational modes, probably reflecting pattern separation and pattern completion, in response to the same event.

The second topic of interest looked at the degree of resemblance of the retrieved information to the original event. We developed paradigms to manipulate realistic memory (Ludmer et al. 2014) and discovered that the computational strategy recruited by the hippocampus depends on the internal state of the participant, whether naïve or distrustful at the start. We also delved into the behavioral and brain mechanisms that mediate the remarkable distortion of an individual's memory engendered by social conformity (Edelson et al. 2011, 2014, 2015). We found that engagement of the amygdala and amygdala-hippocampal functional connectivity at the time of potential social influence predicts subsequent memory distortion. Furthermore, only part of the distortion can be reversed, via engagement of frontal areas, when the social pressure is lifted. We also identified the role of oxytocinergic neuromodulation in this social distortion of memory. Given that humans are social animals, it is important to understand that a significant part of what we believe we know, in fact, is a product of the amalgamation of the views and memories of others. Personal memory hence may be considered conceptually as a node in a distributed memory space that transcends the personal. This may provide us with a phylogenetic advantage in that, on the one hand, accumulated information can be fitted to the real-time requirements of the locale, but on the other, the capacity and availability of information markedly exceeds the capacity and life span of the individual.

## On Drives and the Taxonomy and Frequency of Discoveries

I started my independent research in studying the memory of flies, with the loudly declared and only loosely believed assumption that this ultimately would contribute from the bottom up to the dissection of brain mechanisms of human memory, and decades later, I have found myself dealing directly



with human memory. During this period, the neuroscience of memory has advanced tremendously (Dudai and Morris 2013; Kandel et al. 2014) to include novel stunning methods, as well as brilliant ideas for how to use them. The pace of data accumulation is almost unbelievable. It would have been difficult, if not impossible, to write now my 1989 monograph, at least not without leaving out most of the findings and concentrating on only a few big questions.

This conclusion reflects two developments. First, in my view, it is impossible for a single individual to genuinely master all or even most of the knowledge in their discipline, unless the definition of discipline becomes narrower at an alarming pace. Did I say “master”? Even seriously keeping up with the literature becomes impossible, and the most we can do is file some of the relevant papers under “to read,” primarily as a defense mechanism to pacify the revolting professional conscience. Second, and even more profoundly, it is highly questionable whether we still can grasp the full picture of our discipline, let alone comprehend it. This task seems to far exceed the capability of a single brain. And what is the meaning of comprehension or understanding in science? Recently, I devoted a special topic seminar series at NYU to the question of “what is the meaning of ‘understanding’ in the brain sciences?” The participants, including seasoned experimentalists and modelers, tended to agree that understanding requires a mental model that combines both mathematics and intuition. Even if we feed the mammoth amount of data that we collect into a computer, we may get some solutions and generalizations, *deus ex machina*, but the epistemic opacity of the nonlinear, multidimensional computations done on the computer may hinder not only the joy of personal discovery but also the ability to intuitively grasp what is going on (Dudai and Everts 2014). In other words, the neuroscience ahead of us presents the newcomer to the field with cognitive and emotional demands and personal expectations that are different from those that many of the authors in this volume were facing at the beginning of their careers. One possibility is that neuroscience needs increasingly more phenomenologists, as in theoretical physics, in which experts try to dissociate themselves from collecting data and only think big. The rise of computational neuroscience signals that this is a useful direction for the discipline. This direction requires many biologists to reconsider the attitude that whoever doesn’t produce data is a different species, and for some computational neuroscientists to reassess their belief that seriously consulting the biological data is a superfluous luxury.

Our knowledge about mechanisms is now orders of magnitude more extensive and richer and more exciting than it was 25 years ago. The deeper we go, however, the more we may have to reassess some basic assumptions. Consider just one example: is synaptic plasticity indeed the engine of memory storage, or only of its encoding or expression? My own stand on the big questions is that because memory is the study of experience-dependent

alteration in information, to understand it, we need to understand the brain code of internal representations, including the “machine language” and its computations. The \$64,000 question (devaluation notwithstanding) is inseparable from the central question in brain research in general: what language(s) does the brain speak, and what does it compute in this language? I also believe that this search must involve concerted efforts of many subdisciplines of neuroscience to ensure that pretty models are reflecting what the brain really does and that pretty experiments do not lure us away from feasible models.

In my career thus far, I have sacrificed a few persistent long-term reductionist excursions into molecular mechanisms, using disciplines in which I was trained formally, in favor of behavioral, brain, and more recently, social mechanisms, delving into formal disciplines that were initially more of a terra incognita for me. What navigated these decisions? Recollection is mental time travel into the past, whereas reality is concrete traveling, guided by implicit or explicit mental time traveling into the future. Although postfactum interpretations may not necessarily reflect the critical factor in real-time decisions, they sometimes make sense as more integrative information becomes transparent to the narrator. I am tempted to take on two examples. Why did I decide to apply for only one postdoc position, contemplating reconsideration of my career if the application proved unsuccessful? I may have navigated myself into a test, to see whether the unknown institution that I identified as top-notch accepted me. It was not lack of confidence; it was a reality check. I recommend idiosyncratic reality checks to my students when they finish their thesis and consider a career. I was also attracted by the unknown—neurogenetic dissection à la Benzer was almost the furthest possible from my thesis topic. I am unabashedly inclined to become increasingly bored by paths I traverse. This terrible trait is consistent with my tendency to slowly deviate from the molecular level of analysis. And, on top of it all, I became explicitly and increasingly aware over the years that the drive to understand humans is for me stronger than the drive to understand flies and rodents.

In the career path that we select, we also are driven by interim rewards. How frequently do they arrive? I am not talking about the routine ones, like enjoying a clean electrophoretogram, nice behavioral data, a convincing functional image or a clear-cut statistical significance. I also am not talking about acceptance of a paper for publication in a high-profile journal. I am talking about what we deem as major findings, the adult equivalent of that mini-epiphany that I experienced in the understanding of evolution in high school. How frequent do these findings occur? I tried to estimate and counted seven or eight in my career. They are hidden in the previous text and in my list of publications. This means that I ended with, more or less, one private aha moment every five years or so. As I’ve said, to be a scientist, you must prepare for delayed gratification.

## Epilogue: On Reminiscence Bumps

Upon rereading this essay, I note that in terms of space I did cover the various chapters in my scientific career reasonably proportionally, but the early chapters may seem a bit more colorful. This is the reminiscence bump: the tendency of older adults to have increased recollection, in terms of details and emotions, for events that occurred during their adolescence and early adulthood (Berntsen and Rubin 2002; not to be confused with the sense of well-being that increases after age 50, Stone et al. 2010). Hence, even in writing one's scientific autobiography, one may find oneself either confirming or refuting a scientific model. The aforementioned observation should not belittle the color and emotions of the later chapters of my life. It is only that some of the later events, exciting as they were, lacked the kick of novelty, some became skills and habits, and still others had to do with more time allotted to administration rather than to real science. But one type of reward is sometimes replaced by another. At the Weizmann Institute, I was dean of the Faculty of Biology for six years and chair of the Department of Neurobiology and of the brain research centers for another six years. When I was appointed dean, Benzer dropped me a note, claiming that I should have followed the advice of his colleague, Max Delbruck, to fail on one's first administrative assignment. Science administration does have its own merit, though. My main job was to recruit new faculty that are more knowledgeable than I am. I see them now in labs, corridors, and seminar rooms. In the endless expedition cycles of the scientific culture, their personal chapters are now consolidating.

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