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May 4, 1941

Education:

Oberlin College, BA (1963)
Massachusetts Institute of Technology, PhD (1968)

Appointments:

Fellow, Albert Einstein College of Medicine (1968–1970)
Assistant Research Psychobiologist to Distinguished Professor, Department of Psychiatry, University of California, San Diego (1970–Present)
Research Career Scientist, Veterans Affairs Medical Center, San Diego, California (1980–Present)
Distinguished Professor of Neurosciences, University of California, San Diego (1993–Present)
Distinguished Professor of Psychology, University of California, San Diego (1996–Present)
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Elected, National Academy of Sciences, USA (1993)
Elected, Society of Experimental Psychologists (1993)
Distinguished Scientific Contribution Award, American Psychological Association (1993)
Dana Foundation Award for Pioneering Achievements in Health (1993)
President, Society for Neuroscience (1993–1994)
William Middleton Award, Department of Veteran Affairs (1994)
McGovern Award, American Association for the Advancement of Science (1994; 2004)
Karl Spencer Lashley Award, American Philosophical Society (1994)
Elected, American Academy of Arts and Sciences (1996)
Elected, American Philosophical Society (1998)
Elected, Institute of Medicine (2000)
Metropolitan Life Foundation Award for Medical Research (2000)
Kuffler Lectures, University of California, San Diego (2005)
Howard Crosby Warren Medal, Society of Experimental Psychologists (2007)
Doctor Honoris Causa, University of Basel, Switzerland (2010)
NAS Award for Scientific Reviewing, National Academy of Sciences (2012)
Goldman-Rakic Prize, Brain & Behavior Research Foundation (2012)
Doctor Honoris Causa, Oberlin College, Oberlin, Ohio (2013)
Lifetime Contribution Award, National Academy of Neuropsychology (2017)

Larry Squire has been a pioneer in elucidating the structure and organization of mammalian memory. He provided the first evidence that the resistance of memory to disruption can develop over a period of years in humans. This finding implied a memory consolidation process that reflects, not rapid transition from a labile to a stable, long-term state but gradual reorganizfation within long-term memory itself. He showed in rats, monkeys, and humans that, by such a process, memory becomes gradually independent of the hippocampus and intrinsic to neocortex. With Stuart Zola, and working with nonhuman primates, he discovered the anatomical components of the medial temporal lobe memory system: the hippocampus plus the adjacent, and previously neglected, entorhinal, perirhinal, and parahippocampal cortices. Building on early work with his student Neal Cohen, he established the biological distinction between declarative and nondeclarative memory and the idea that different kinds of memory depend on different brain systems. Through studies of memory-impaired patients, classical eyeblink conditioning, and memory-guided eye movements, he and his colleagues identified conscious awareness as key to the distinction between declarative (aware) memory and nondeclarative (unaware) memory. The work is a rare example of bringing both human and animal studies, and multiple methods, to the science of brain structure and function.

Larry R. Squire

There was nothing particular in my background to suggest that I might become a scientist. Both my parents and all four grandparents were from Grinnell, Iowa. My maternal grandfather was a longtime professor of speech at Grinnell College, and my maternal grandmother was an accomplished pianist and harpist. My father's circumstances were more modest. His father ran a gas station, and my father worked his way through Grinnell College, majoring in physics. The family left Iowa for New Jersey and then New York State soon after I was born and a few years later landed in Columbus, Ohio, where my father founded a successful, wholesale heating and air conditioning company. At one point he served as president of his national trade association. Later in life, leaving the daily tasks of the business to others, he attended Ohio State University to obtain a doctorate in finance, taught a course at a local university for many years, and produced two instructional books for contractors in retail business. We took a number of camping trips, together with other boys, including one epic trip down the Ohio and Kentucky rivers. My father and I were both Eagle Scouts. He was always an advocate of hard work and had strong opinions, but as a Goldwater Republican his opinions usually differed from mine.

My mother was more easygoing. She ran the house and looked after my younger sister and me. She enjoyed sports (had a basketball trophy from high school), did ceramics, and had a talent for word games. All through high school, I could never beat her at anagrams or categories (write down city names, rivers, birds, and so on beginning with a particular letter). She was completely noncompetitive. I beat her once when I prepared for a game of categories by studying the dictionary and then suggested that we use the letter *R*. When I won, she made no comment and seemed not to notice that anything unusual had happened. Once she attended a baby shower for a niece and joined in a game of anagrams (make as many words as possible from some longish title words). After several minutes, the hostess asked, "Does anyone have more than 20?" "Oh, I have about 200," my mother said. She explained to me later, "They gave you all the vowels."

Early Schooling

My mother took a close interest in my early schooling where, as an early reader, I was mostly unengaged. After I skipped the second half of first grade at public school, she enrolled me in the supposedly progressive university

school, affiliated with Ohio State. There, the class was divided into three reading groups—advanced, middle, and slow. Still the early reader, I was assigned to tutor the slow group. I have always viewed this as unfortunate, because it set me apart from the other students and encouraged the idea that I had special academic talent. In fact, as I later learned, reading skills develop at different rates, and the slower kids turned out fine. In any case, my mother had had enough and with third grade I began at the Columbus Academy, a private day school for boys (grades 1 through 12). I liked it there. The teachers were excellent, and I was glad to be in the midst of very capable students.

At the Academy, the junior year public speaking course required each of us to deliver a talk to the student body. As I rose through the grades, hearing splendid talks on such subjects as the United Nations, bats, and the ascent of Mt. Everest, I harbored the idea that I would transfer to a different school that year. The thought of speaking in front of a couple hundred people was terrifying. When my time came, I proposed the topic "Science and Religion." Fortunately, the instructor was discouraging ("a bit too large"), and in the end, I managed to deliver on the topic of hypnosis, perhaps an early sign of interest in cognitive science.

I had no real plans for college except to go to a good place that was coeducational. (In 1959, most of the noted east-coast schools enrolled only men.) One day my mother came across a ranking of the top 10 schools in my category. The list began with Oberlin, then Swarthmore, and then others including Reed, Grinnell, and Carlton. Oberlin was first, so I visited and then applied only there. It proved to be a fine choice. The faculty was dedicated and accessible, music was everywhere (thanks to the Conservatory of Music), and the students were a stimulating mix of impressive and interesting people (many from the east coast) who, like me, had opted for a small, active community over a larger school with clubs and fraternities. Among the faculty, I was most influenced by Norman Craig (chemistry), Lee Henderson (psychology), and Celeste McCollough (psychology), discoverer of the McCollough visual aftereffect. She taught a riveting course in what was then called physiological psychology. Neuroscience was not yet a curriculum term.

Graduate School

When it came time to think about what to do next, I recognized that I was deeply interested in brain and cognition. If I were going to learn more, I would need to go to graduate school. I did not have enough background at that point to suppose that I was preparing to be a scientist. Rather, I imagined becoming a scholar, an academic, perhaps a professor at a place like Oberlin.

The direction I was headed in looked even better after spending the summer after Oberlin (1963) as an assistant to Dr. McCollough, who was

doing a sabbatical term at McGill University in Montreal. I undertook a largely unsuccessful project involving autonomic conditioning in the rat, but I was able to meet Donald Hebb, Peter Milner, and a number of talented graduate students, including Graham Goddard and Philip Liss. The highlight of the summer was a visit from Jerzy Konorski, director of the Nencki Institute of Experimental Biology in Warsaw and author of the 1948 book *Conditioned Reflexes and Neuron Organization*. He gave a chalk talk, and the students told him about their projects. I had no experience in presenting but was asked to take a turn as well, so I told him about my project, which had no results. He listened politely, hurrying me along when I described irrelevant details and expressing interest in the overall idea. I returned from McGill through Washington, D.C., where I participated in the March on Washington and heard Martin Luther King deliver "I Have a Dream." The eloquence of his address distinguished it from the many other speeches made that day, but only later was I able to appreciate that I had been present at an historic occasion.

I was accepted at the three graduate programs I applied to and had decided on the Department of Psychology at Stanford. I was especially interested in memory and knew of two faculty there, J. Anthony Deutsch and Karl Pribram, who had written on the subject. As it turned out, Tony Deutsch was not working on memory at the time, and Pribram was remote in the medical school. There were fine faculty, and a large clinical program, but there was nothing resembling neuroscience and no program for the biological side of psychology.

I did find a card room and fell into regular poker playing (no limit, California lo ball). This was pretty absorbing, and I was good enough at it to match my stipend. But, by the end of the year, I had not connected to any faculty except a prominent neuroendocrinologist, Seymour (Gig) Levine, who was a regular at the card room and known to us there simply as "Doc." I only learned who he actually was later in the year when one day I saw him parking near the building where he was to chair our group's weekly lunch meeting. I greeted him with "Doc, do you work around here?" Such was the extent of my disconnection from Stanford. At the year-end evaluations, I was 1 of 9 in our class of 27 who was invited to stay one more year for a terminal master's degree.

Someone asked me once why I didn't give up at this juncture, but I guess this didn't occur to me. Stanford at the time was not a good match for my interests, and in truth, I hadn't yet really engaged in graduate school. After a couple weeks of disorientation and reflection, I wrote to MIT where I had been accepted initially and asked if I might "reactivate" my admission after I completed the master's degree. In what proved to be the signal event of my career, I soon received a letter saying to forget the master's and that I could come in the fall. So, in 1964, off I went to Cambridge. From Stanford, I took my poker winnings and the beginnings of what became a lifelong hobby.

MIT was what I had hoped for. The program was housed in a single building, there was considerable *esprit* among the students, and there seemed to be a sense of common purpose across the entire community. Everyone's work was relevant and interesting, and most of it involved what would soon be called neuroscience. The faculty included Peter Schiller (see Volume 7 in this series), Charlie Gross (Volume 6), Richard Held (Volume 6), Emilio Bizzi (Volume 6), the distinguished neuroanatomist Walle Nauta, and a research associate, Harvey Karten. The department head Hans-Lukas Teuber, a remarkable man, had assembled the faculty himself (then as a Department of Psychology, later renamed the Department of Brain and Cognitive Sciences). He had encyclopedic knowledge of the literature and was a gifted lecturer. The weekly Friday colloquia, which drew scientists from the Boston area, appeared to be organized entirely by Teuber, and he introduced most of the speakers himself. He inspired a whole generation of students to pursue what now would be called systems neuroscience (cellular and molecular neuroscience came to the department later). He died in 1977 in a swimming accident at the age of 60.

At MIT, I made some missteps as I learned what was expected of a graduate student and a young professional. On one occasion, the department scheduled a practice session for the people who would be speaking at an upcoming meeting. Afterward, one of the faculty asked me, "Why weren't you there?" "Well," I said, "I know what everyone is doing." He patiently explained that the purpose of the session was not for my benefit but for me and others to provide feedback and encouragement to the speakers. On another occasion, I attended a large meeting where a speaker was to present on spreading depression, a technique I had used but with a different interpretation (Squire and Liss, 1968). After the session, one of my faculty found me and asked, "Where were you?" I replied, "I know his experiments and what he was going to say, so I went to another session I was interested in." With some dismay, he explained that I needed to be there to represent my position and potentially defend it. All of this seems so obvious now that it is difficult to recognize myself in these stories.

I eventually developed a project documenting the effects of cholinergic and anticholinergic drugs on memory in rats (Squire, 1969). It was not unusual in those days for graduate students to construct their thesis problems semi-independently and outside the research program of any particular faculty. Peter Schiller kindly agreed to be my adviser, despite not being especially interested in my topic. Professor Teuber seemed eager to see me finish ("You did have that extra year at Stanford") and suggested that I visit Murray Jarvik, professor of Pharmacology at the Albert Einstein Medical School, as a possible postdoctoral opportunity. I did, and Murray offered me a place in his lab funded by an Interdisciplinary Fellowship program. So, in 1968, after completing my doctorate under Schiller, I relocated to New York City and Einstein, where Murray told me I should work on whatever I liked.

Einstein

I began at Einstein with studies that continued my thesis topic, but in my first year I had the good fortune to meet Samuel Barondes, associate professor in the Department of Psychiatry. Sam's lab was conducting in mice some of the first behavioral studies showing the importance of brain protein synthesis for the formation of long-term memory. The work involved inhibitors of protein synthesis, such as cycloheximide and anisomycin, and behavioral tests of memory. Sam was a master of efficiency who aimed at the heart of questions with simple experiments. I saw this work as getting at the nature of memory more directly than what I could do with my cholinergic drugs. After a few conversations, we began to collaborate. The experiments in Murray's lab continued, eventually yielding three publications, but my enthusiasm had been redirected. The initial efforts with Sam resulted in one paper in *Nature* and another in *Science* (Squire and Barondes, 1970; Segal et al., 1971). Sam's talent for formulating questions and presenting a coherent story was on grand display. In our study of actinomycin-D, an inhibitor of RNA synthesis, the behavioral experiments ran afoul of the toxic effects of the drug. After several efforts, I came to his office with news of the final failure, expecting some mutual commiseration and an abandonment of the project. I knew that we would not be able to say anything compelling about RNA synthesis and memory. Sam said, "Let's run another group so we can make a different point [memory changes with time] and send it to *Nature*."

In the midst of all this, Sam was recruited to the new Department of Psychiatry at the University of California San Diego (UCSD) and invited me to join him. I was familiar with the area because my maternal grandparents had earlier retired to La Jolla for a number of years, and my family had made several cross-country automobile trips to visit them during the late 1940s and early 1950s. So, in 1970, I made the easy decision to move, taking a research scientist position in Sam's group.

Arriving at UCSD

Collaborative studies with inhibitors of protein synthesis continued with Sam at UCSD and resulted in six publications that described the behavioral actions of the drugs and ruled out various side effects. Even after I obtained an independent position in 1973 (supported by the Veterans Affairs Medical Center) and began working with humans, I did some additional work with the inhibitors, publishing eight papers. Yet one could see that, although much had been learned, this particular approach (drugs and behavior) could take us only so far with the tools available at the time. Moreover, concerns about side effects continued to appear in the literature, despite our efforts to address a number of them directly (Squire et al., 1974; Squire et al., 1976b). With the idea that the story was

nevertheless on pretty strong footing, Hasker Davis (a former undergraduate in the lab) prepared a review with me to summarize the case for the importance of brain protein synthesis, during or shortly after training, in the formation of long-term memory (Davis and Squire, 1984). I have always been glad, as Sam and I turned to other topics, that there was an opportunity to do a thorough accounting of where the problem stood at that point. The paper has accumulated more than 1,600 citations. Many years later, an excellent review made the case again, and more comprehensively, revisiting the matter of side effects and drawing on evidence from newer methods for disrupting protein synthesis (Alberini, 2008, *Neurobiology of Learning and Memory, 89*, 234–246).

The Move to Studying Memory in Humans

What propelled me to human work was a 1971 publication on retrograde amnesia in a mixed group of five memory-impaired patients (Sanders and Warrington, 1971, *Brain, 94,* 661–668). Retrograde amnesia refers to memory loss for information that was acquired before the onset of memory impairment. The patients in that study had memory loss (for past news events and famous faces) that extended into the past across the three to four decades that were measured, and its severity was similar at all past time periods. This result completely perplexed me. It did not fit with what I had come to understand from the animal literature, in which retrograde amnesia was typically brief and also temporally graded, affecting recent memory more than older memory. Retrograde amnesia in animals was thought to provide evidence for memory consolidation: the idea that memory is initially in a labile state but becomes fixed and less vulnerable to disruption as time passes after learning.

At the time, there was active interest in how long it takes after learning for this fixation process to occur. The animal work suggested a time frame of seconds, minutes, or hours, perhaps reflecting the transition from a fragile short-term memory to a stable long-term memory. I also had been intrigued by a few clinical reports that patients can sometimes exhibit retrograde amnesia extending back a few years. However, the evidence for such prolonged, but still temporally graded, memory loss was weak, and the idea did not attract much attention. When an interview about the past covers a period of years, questions about the remote past tend to query salient events that have proved resistant to forgetting, whereas questions about the recent past query less salient events that may be soon forgotten (in the extreme, "What was the name of your first school?" vs. "What did you have for breakfast today?"). As a result, when a patient appears to have lost mainly recent memory, one cannot know whether the patient really has temporally graded memory loss for the past or whether the patient simply has lost the weaker memories.

The First Experiments: Memory Consolidation

I began by asking if long gradients of retrograde amnesia covering a year or more can actually occur. What was needed, I thought, was a method to sample past events equivalently—that is, a method to assess information from past time periods that had initially been learned to the same extent. After six months of trial and error, we developed a memory test for the names of television programs that had broadcast for a single season, 1957–1972 (Squire and Slater, 1975). The correct answers (five items/year) were the names of one-season programs, and each program was presented together with three fabricated titles. Popular exposure to the programs across time periods was quite similar, based on data from the Nielsen Company for percent of households having a television, percent time watching television, and individual ratings for each program. Moreover, program names were apparently learned close to the time the programs were on the air, because high-school students failed to recognize the names of programs broadcast when they were very young, and adults residing outside the United States for a period of years were poor on questions about programs broadcast while they were away.

Being in a Psychiatry Department, I was aware that a number of facilities in the area offered electroconvulsive therapy (ECT) as a treatment for depressive illness. ECT seemed to provide a perfect way to study the temporal dimension of retrograde memory loss. Indeed, electroconvulsive shock, or ECS as it was called, was at the time the most widely used method for studying retrograde memory in rodents. We gave half the test to patients a day before their first treatment and the other half 1 hour after the fifth treatment at a time when memory impairment is readily detected. The results were straightforward. Before ECT, recently broadcast programs were remembered better than programs broadcast many years ago (evidence for normal forgetting). After ECT, memories acquired up to three years before treatment were markedly impaired, but more remote memories (4 to 17 years old) were fully spared (Squire et al., 1975). Moreover, the performance score after ECT for the most recent few years was not just low but lower than the scores for any of the more remote time periods. This particular result, that recent memory was even poorer after ECT than more remote memory, was the key feature of the data that made the findings relevant to memory consolidation (see Squire, 1992, for elaboration of this point). In subsequent work, we found a similar pattern of memory loss when we asked about the temporal order in which the programs had broadcast (Squire et al., 1976a) or asked patients to recall details about the programs (Squire and Cohen, 1979).

These findings provided the first evidence that resistance of memory to disruption can increase over a lengthy time period (a few years). Thus, the same kind of experiment that in animals had suggested a brief period of consolidation, and a rapid transition from a labile to a stable state, now

suggested that consolidation depended on reorganization within long-term memory itself. The process proceeds such that the same material that is becoming harder to recall (through normal forgetting) is also becoming less vulnerable to disruption.

I wondered why these findings in humans were so different from the finding of very brief retrograde amnesias in rodents. So a few years later, we did a large study with ECS in mice (Squire and Spanis, 1984), giving ECS four times at 1-hour intervals to mimic the multiple treatments in humans that had yielded a few years of retrograde amnesia. We gave ECS at one of seven different delays (1–70 days) after training on a one-trial task, and tested retention two weeks after treatment. Control animals exhibited gradual forgetting with increasing retention intervals. ECS caused extended retrograde amnesia covering the period one day to three weeks prior to treatment. Memories acquired three to ten weeks before treatment were fully spared. These findings increased by an order of magnitude the time period across which temporally graded retrograde amnesia had been demonstrated in rodents, presumably as a result of using a strong amnestic protocol. The results showed that in mice, as in humans, the process during which memory becomes less vulnerable occurs within long-term memory. Perhaps it was a coincidence, but we also noticed that the percentage of life span covered by these longer retrograde amnesias was similar in the two species.

Clinical and Practical Studies of ECT

When I was studying ECT in the 1970s, I discovered that a number of practical questions about how a course of ECT affects memory had not been addressed as thoroughly as they might. How long after ECT does memory impairment last? Are any effects permanent? How do patients rate their memory abilities as time passes after treatment? We were well equipped to pursue these questions. Moreover, this was the kind of thing that the psychiatrists who were giving us access to their patients really wanted to know. The first study simply compared the new learning ability of 38 patients who, six to nine months earlier, had had a course of bilateral ECT (mean = 10 treatments), right unilateral ECT (mean = 9 treatments), or hospitalization without ECT (Squire and Chace, 1975). Fifteen inpatients currently receiving bilateral ECT were also tested during their course of treatment to provide a profile of memory impairment against which follow-up performance could be compared. On six tests of recall and recognition (both verbal and nonverbal), the inpatients currently receiving bilateral ECT were markedly impaired, but the two follow-up groups tested six to nine months after ECT performed virtually the same as the inpatients who had never received ECT. The tests were sensitive enough to detect the weakening of memory that occurs from one decade to the next during normal aging. Interestingly,

and despite their good performance, 10 of the 16 patients in the bilateral group expressed persistent complaints about their memory abilities. In other tests of new learning, bilateral ECT always disrupted memory more than right unilateral ECT (Squire, 1977).

In a different study, we assessed retrograde memory loss by giving four tests involving public events or personal memories on three occasions: before bilateral ECT, one day to one week after the completion of treatment, and about seven months later (Squire et al., 1981). ECT initially disrupted past memories as measured by all the tests. As time passed, the retrograde amnesia shrunk, as had been described in the clinical literature, for example, after head trauma. By seven months after ECT, recovery was nearly complete with the exception of persistent memory loss from the period several days to possibly a few weeks before treatment. We later demonstrated shrinkage of retrograde amnesia with formal tests in other kinds of transient amnesia—after ECS in mice (Spanis and Squire, 1987) and after TGA (transient global amnesia) in patients (Kritchevsky and Squire, 1989). In the case of TGA, we estimated the permanent retrograde loss to cover several hours to days; in the case of mice and ECS, we estimated one to five days.

Some insight into what explained patients' persistent memory complaints, despite all the evidence of recovery, came when we constructed tests to get at this quantitatively (Squire et al., 1979; Squire and Slater, 1983). For example, we presented a horizontal bar marked into time bins, including "now" and "time of ECT," and asked patients to indicate what time periods they had difficulty remembering. Although there was considerable variability, 31 patients who had received bilateral ECT three years earlier indicated a median of two months of anterograde amnesia and six months of retrograde amnesia. What was interesting about this was that the patient descriptions, on average, resembled what we had measured with our objective memory tests. In the case of retrograde memory, we had identified some persistent loss of the past from the period just before treatment. In the case of anterograde amnesia, the capacity for new learning did improve and gradually recovered during the weeks and months after treatment. However, memory for the period shortly after ECT, when new learning was affected, did not return, presumably because these memories had not been established in the first place. I also proposed an additional factor that I thought might contribute to complaints about memory. As time passes after treatment, and memory improves, it may become increasingly difficult to discriminate the ordinary lapses and failures of memory that are part of daily life from failures attributable to ECT.

As a result of our ECT work, I was invited to participate in a number of panels and symposia, including a Task Force on ECT (1975–1978) organized by the American Psychiatric Association. In these formats, I was usually the lone representative of the "costs" of ECT in the context of broader

discussion of safety and efficacy. Often, I found myself somewhere between the treating psychiatrists, who hoped for as little memory impairment as possible, and patient advocates, who thought that blaming any part of memory complaints on ordinary lapses in memory rather than on ECT was tantamount to saying, "It's all in your heads." I remember speaking at a National Institute of Mental Health (NIMH) Consensus Conference in 1978, which was open to both academics and lay people, where I had the unique experience of hearing a hiss from the audience as I discussed the thorny issue of memory complaints.

Bringing in Neuroanatomy

With the development of modern imaging techniques, especially structural magnetic resonance imaging (MRI), it became possible to bring neuroanatomy to our studies, including the study of the long consolidation process that had been revealed by ECT and ECS. I had always believed that neuroanatomy was critical for studies of memory-impaired patients so as to relate patient work to animal work, and for moving the whole enterprise in the general direction of biology. We began these efforts with Gary Press, then a neuroradiologist at UCSD, and David Amaral, a fine neuroanatomist who was then at the Salk Institute. The first success was a high-resolution protocol for imaging the human hippocampus, which we accomplished by obtaining images precisely perpendicular to its long axis (Press et al., 1989). None of us had ever seen the human hippocampus with such clarity in a living person, and I don't believe anyone had. I guess *Nature* thought so, too, as they put a coronal image on its cover showing a beautiful left and right hippocampus belonging to one of my graduate students. Seeing the first images appear on the monitor was one of those exhilarating scientific moments that one remembers forever. This development meant that we could now identify (and measure) volume loss in patients whose memory impairment resulted from hippocampal damage (or larger medial temporal lobe damage) and also could distinguish these patients from patients with diencephalic amnesia, such as Korsakoff syndrome (Squire et al., 1990).

During the same time period, we had begun to assemble a small population of memory-impaired patients with selective hippocampal lesions whom we could characterize with these methods. This meant we could move to studying memory in these patients instead of in patients receiving ECT. Our first studies of retrograde amnesia with this group found temporally limited retrograde amnesia (for past news events and famous faces), but the questions we had constructed were grouped by decade and did not have good temporal resolution (Squire et al., 1989; Reed and Squire, 1998). We could not use the television test because viewing statistics had become less stable from year to year, as television moved from broadcasting on only three channels to broadcasting on multiple channels.

Instead, graduate student Joe Manns put together several hundred questions that asked participants about notable news events that had occurred in a particular year from 1950 to early 2002 (Manns et al., 2003). Testing proceeded in a free-recall format, and the data for each patient were analyzed according to the year the patient developed memory impairment. In this way, a score for each patient was calculated for the period of anterograde amnesia and, in five-year intervals, for the period of retrograde amnesia up to a maximum of 30 years (mean = 32 questions for each time period). On this test, the patients with damage thought to be limited to the hippocampus were impaired at recalling events that had occurred after the onset of their amnesia and for the period one to five years before amnesia. Memory for more remote events was intact. Christine Smith joined the lab as a postdoc at about this time (and stayed on to become an invaluable colleague and leader of many projects, eventually with her own faculty position). Using the same news-event questions and fMRI, Christine found gradually decreasing activity in the hippocampus as participants recollected events from 1 to 12 years ago and a constant level of activity during recall of more remote events from 12 years up to 30 years ago (Smith and Squire, 2009).

These findings supported our developing idea that the hippocampus has a time-limited role in the formation of memory (Squire, 1986, 1992; Squire and Alvarez, 1995), an account that is sometimes referred to as the standard model of memory consolidation. After learning, the hippocampus initially works together with distributed sites of memory storage in neocortex, but as time passes, the role of the hippocampus gradually diminishes and a more permanent memory is established in the neocortex. The idea is not that memory literally transfers to the neocortex, for information is encoded in neocortex as well as in hippocampus at the time of learning. The idea is that gradual changes in neocortex increase connectivity among the cortical regions that ultimately store the learned material. These changes eventually allow the neocortex to support recall on its own without the participation of the hippocampus. To make the basic point more concrete, we constructed a simple network model that behaved in a way that was consistent with the data (Alvarez and Squire, 1994).

There was initially skepticism about the idea that such a process could continue for years, although I did point out that forgetting itself can proceed over even longer time periods (Squire, 1989). Later, we began to study the matter prospectively in animals with hippocampal lesions and found long gradients of retrograde amnesia, just as we had found earlier with mice given ECS. In rats, the gradient extended across 30 days (Clark et al., 2002a); in monkeys, eight weeks (Zola-Morgan and Squire, 1990). The monkey study was especially satisfying because it was one of the first such studies and was the only study on this problem ever done in monkeys. It required scheduling multiple events across the calendar, all in advance of an outcome that

we would not see for several months. Monkeys learned 100 simple object discriminations beginning 16, 12, 8, 4, and 2 weeks before surgery (20 object pairs per time period). After surgery, we assessed the status of object memory by presenting each of the 100 object pairs for a single choice trial.

Following the monkey work, a number of groups in the 1990s found long gradients of retrograde amnesia after hippocampal lesions in mice, rats, and rabbits. It is now widely appreciated that, in rodents, the time needed for memory to become independent of the hippocampus is about 30 days. In our monkey study, it was eight weeks, and in humans it was a few years. I have supposed that the process develops more slowly as one moves from simple to more complex nervous systems. In any case, we knew now that memory consolidation, as studied in our own work on retrograde amnesia, was never about a transition from a short-term (labile) to a long-term (stable) memory but described a gradual process during which memory becomes independent of the hippocampus and is consolidated in neocortex. This process is now often referred to as systems consolidation to distinguish it from the cellular-level (consolidation) process that depends first on changes in synaptic strength and then on protein synthesis and morphological change. An excellent review summarized where things stood with systems consolidation at that point (Frankland and Bontempi, 2005, *Nature Reviews Neuroscience*, *6*, 119–130). Ten years later, in collaboration with Richard Morris and others, we wrote a review as well (Squire et al., 2015).

It turned out that about 30 years following the 1971 publication in *Brain* that had brought me to the study of human memory, I could understand their report of an ungraded retrograde amnesia that extended decades into the past. It's all in the anatomy. First, none of the patients in the 1971 study had the restricted, bilateral hippocampal damage that we had found to result in only a few years of retrograde amnesia. One of these early patients proved to have left lateral hippocampal damage together with a right temporal lobectomy that left intact only part of the right superior temporal gyrus. Another had had coal gas poisoning, and three had Korsakoff syndrome, a form of diencephalic amnesia. Second, extended retrograde amnesia across decades can occur when the lesions extend beyond the hippocampus into the adjacent structures of the medial temporal lobe as in patients E. P. and G. P. (Reed and Squire, 1998; Bayley et al., 2006). In these cases, retrograde amnesia covered as much as 30–50 years (but with substantial sparing of very remote memories from adolescence and young adulthood). Third, retrograde memory loss can extend even into childhood when the pathology involves most of the medial and also lateral temporal lobe bilaterally (patient G. T.), or the medial temporal lobe plus areas of temporal and frontal neocortex (patients H. C. and P. H.) (Reed and Squire, 1998; Bayley et al., 2005b). Indeed, unlike any other patients we have studied, G. T. and P. H. were unable to recall a single autobiographical memory from early life, perhaps because their cortical damage directly disrupted sites of long-term

memory storage. This all added up to the simple idea that there is not a single phenotype of retrograde amnesia or a single "amnesic syndrome" but rather different phenotypes of retrograde amnesia and different presentations of memory impairment, all dependent on neuropathology.

Other reports of impaired autobiographical recall from childhood often have included the suggestion that hippocampal damage itself is responsible. The proposal is that autobiographical information (but not factual information) depends on the hippocampus for as long as a memory persists. I have been sour about this idea and have not found compelling evidence for it. To be incapable of any autobiographical remembering takes a lot more than hippocampal damage. Such an impairment requires a patient such as G. T., with his large medial and lateral temporal lobe lesions, or the head trauma patient K. C., with his medial temporal lobe lesion and widespread neocortical damage, who was well described by investigators in Toronto (Tulving et al., 1988, *Brain and Cognition*, *8*, 3–20).

Our own three studies of autobiographical memory found intact recollection of remote autobiographical memories after hippocampal lesions, even after large medial temporal lobe lesions, together with impaired recollection of recent memories (Bayley et al., 2003; Kirwan et al., 2008a; Dede et al., 2016a). We tried to sort all this out in a review (Squire and Bayley, 2007), and I continue to believe that the clearest perspective will come from neuroanatomy and from careful description of the locus and extent of lesions. One also recognizes that the topic of autobiographical recollection itself is particularly challenging, because the available testing methods are a little "soft," and it's unclear how to study the problem in experimental animals.

The best kind of anatomical information, of course, comes from postmortem histological analysis of patients who have been well studied during life. Succeeding at this is difficult and rarely accomplished, as it depends on cooperation from many directions, especially on being able to obtain the brain within hours of death. Nevertheless, we have been pretty dedicated in these efforts, and my group, in collaboration with David Amaral, has been able to present eight cases (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996; Gold and Squire, 2006; Insausti et al., 2013).

An example of the benefits of postmortem data came when Ricardo Insausti and David Amaral carried out a detailed neurohistological analysis for patient E. P., whom we had studied for 14 years (Stefanacci et al., 2000; Insausti et al., 2013). E. P. had developed profound memory impairment after encephalitis, an impairment that proved to be even more severe than in the noted patient H. M. (Scoville and Milner, 1957, *Journal of Neurology, Neurosurgery, and Psychiatry, 20*, 11–21; Squire, 2009). We had studied E. P.'s MRI images, obtained 8 and 12 years earlier, and had noted shrinkage of the lateral temporal lobe. Yet, I was still impressed by the extent to which his entire temporal lobe bilaterally was shrunken and atrophic, probably (as we thought about it) because of loss of afferent input (e.g., from amygdala and

perirhinal cortex) as well as intracortical afferents that funnel through the temporal stem. Loss of afferents from lateral temporal cortex through retrograde degeneration also could have been a factor. It seemed likely to us that some shrinkage within lateral temporal cortex may be a typical (albeit indirect) consequence of large medial temporal lobe lesions, given the substantial connectivity between the medial and lateral temporal lobe. In addition, it is possible that shrinkage within the lateral temporal lobe increased over the years as anterograde and retrograde degeneration progressed. This scenario raised the possibility that the considerable extent of E. P.'s retrograde memory loss, as described earlier (Reed and Squire, 1998; Bayley et al., 2006), could have reflected, at least in part, these changes in his lateral temporal cortex. This means that it is important to evaluate the status of lateral temporal cortex, and the possible contribution of lateral temporal damage, when evaluating patients with large medial temporal lobe lesions. It is also a good idea to obtain MRI data close to the time that neuropsychological and neurohistological data are obtained.

Nonhuman Primates

In 1978, another publication appeared that dramatically altered the course of my work (Horel, 1978, *Brain, 101*, 403–435). Horel proposed that it was not hippocampal damage that impairs memory but damage to temporal stem white matter, which lies just above the hippocampus and connects lateral temporal neocortex to diencephalic and other subcortical targets. The temporal stem, he argued, would necessarily have been damaged by the surgical approach that had been used to resect medial temporal lobe structures in monkeys and in humans, including patient H. M. Horel noted, too, that efforts in rats and monkeys with hippocampal lesions to establish an animal model of H. M.'s condition had foundered up to that point. I had to admit that the case for the hippocampus was not as rock solid as I had thought. I was so eager to jump into the problem that I asked a young graduate student at UCSD if he would like to do a monkey project with me, a ludicrous idea as I knew nothing about monkey work except from reading (he declined). I began making serious inquiries and had the good fortune to hear from Stuart Zola-Morgan (later Stuart Zola), who was just completing postdoctoral work with Helen Mahut in her Boston primate lab and happened to find my letter to Helen, which was sitting neglected on her desk. Stuart came to UCSD, set up a monkey lab, and eventually obtained an independent faculty position. Working with Stuart was one of the great pleasures of my career. It involved almost nightly phone calls to talk through the work and continued for 21 years until he left to become director of the Yerkes National Primate Research Center at Emory University.

In an odd coincidence, in the same year that Horel presented his new idea (1978), Mort Mishkin described a profound memory impairment in

monkeys with large medial temporal lobe lesions, designed to reproduce H. M.'s lesion and using a task, delayed nonmatching to sample (DNMS), that tested memory for single events (Mishkin, 1978, *Nature*, *273*, 297–298). In DNMS, the monkey first displaces a single (sample) object to obtain a reward. Then after a variable delay, from a few seconds to many minutes, the monkey sees the old object together with a new one and receives a reward for choosing the new one. New pairs of objects are used on each trial. The lesion damaged the hippocampus, the amygdala, and adjacent cortex and came to be identified as the H^+A^+ lesion (the plus signs denote that cortex was damaged by the direct surgical approach used to access the hippocampus and amygdala).

This important finding described the kind of memory impairment that one saw in patients and made it possible to ask: What damage within the large territory of this lesion was responsible for the memory impairment? Or, in the light of Horel's novel suggestion, was damage to the white matter of the temporal stem responsible? Our first study, in which Mort joined, simply compared the effects on memory of temporal stem lesions and H^+A^+ lesions (Zola-Morgan et al., 1982). Temporal stem lesions had no effect on DNMS, although they did impair the learning of visual pattern discrimination tasks in which the animal learns which of two patterns is correct (e.g., □ vs. +). The H^+A^+ lesion severely impaired DNMS but spared pattern discrimination learning. The same H^+A^+ monkeys also failed a number of memory tasks in addition to DNMS that patients with medial temporal lobe lesions had failed (Zola-Morgan and Squire, 1985).

We had some ideas about why visual pattern discrimination learning might be spared. Monkeys took as many as 300 trials to gradually learn these two-dimensional pattern tasks, reminding us of the gradual learning of motor-skill tasks and perceptual-skill tasks, which were known by that time to be spared in patients (see the section "Multiple Memory Systems"). In fact, the same monkeys with H^+A^+ lesions who had succeeded at difficult pattern discrimination learning also succeeded at learning motor-skill tasks (Zola-Morgan and Squire, 1984). In contrast, these monkeys were impaired on easy discrimination problems involving distinct, three-dimensional objects that could be learned in only 10 trials. Perhaps learning the easy problems was more like learning a fact than acquiring a skill. The monkeys with temporal stem lesions who had failed difficult pattern discrimination tasks were intact at the easy problems (Zola-Morgan and Squire, 1984). Stuart and I wrote a review during this period, developing the idea that difficult pattern discrimination learning tasks in the monkey were largely skill-like tasks, an idea first suggested by Sue Iversen (*International Review of Neurobiology*, 1976, *19*, 1–49), and making the case for a correspondence between the findings for human and nonhuman primates (Squire and Zola-Morgan, 1983). We argued that the effects of temporal stem damage on pattern discrimination learning reflected visual processing deficits

associated with the loss of afferents and efferents of the unimodal visual area TE in lateral temporal neocortex.

None of us had paid much attention to the fact that the surgical approach used in these studies to target the hippocampus and amygdala proceeded directly through one or more structures of the adjacent parahippocampal gyrus: perirhinal cortex, entorhinal cortex, or parahippocampal cortex (area TH-TF). Indeed, what I am here calling the H^+A^+ lesion was originally termed the A+H lesion, and the plus-sign superscripts were not introduced until several years later (Squire and Zola-Morgan, 1988). The perirhinal cortex, in particular, was barely on the radar, as our graduate student Wendy Suzuki and David Amaral only recently had redefined its borders. Instead of comprising a small area on the lateral bank of the rhinal sulcus, as originally thought, the perirhinal cortex now extended laterally all the way to the medial bank of the anterior middle temporal sulcus in the ventral temporal lobe. These structures of the parahippocampal gyrus would soon prove to be an important part of the story.

At about this time, as our program of human work continued, we had the opportunity to study a patient who became moderately amnesic following an ischemic event in 1978 and was then tested extensively until his death in 1983 (patient R. B.). With the consent of family, we were able to obtain the brain at the time of death, and David Amaral then undertook a detailed histological examination, which revealed a bilateral lesion restricted to the entire rostro-caudal extent of the CA1 field of the hippocampus (Zola-Morgan et al., 1986). This was the first reported case of memory impairment following a lesion limited to the hippocampus in which extensive neuropsychological and neuropathological analysis had been carried out. Here was conclusive evidence that the hippocampus itself was important for memory. In addition, because R. B. was not nearly so impaired as patient H. M., the findings clearly indicated that other areas beyond CA1, most likely outside the hippocampus, must also be important for memory functions. Later, we developed a technique for the monkey that combined stereotaxic surgery with MRI to make substantial lesions of the hippocampus (the H lesion) with little or no damage to adjacent cortex (Alvarez-Royo et al., 1991). These monkeys were moderately impaired on two tasks of recognition memory: DNMS and visual paired-comparison, and (just as R. B. was much less impaired than H. M.) the H monkeys were much less impaired than monkeys with the large H^+A^+ lesion (Alvarez et al., 1995; Zola et al., 2000).

Buoyed by the R. B. case, we next prepared an H^+ lesion in the monkey involving the posterior medial temporal lobe (Zola-Morgan and Squire, 1986). The H^+ lesion was limited to the hippocampus and the underlying posterior entorhinal and parahippocampal cortices, and it unequivocally impaired memory. Comparisons carried out later between the H^+ monkeys and the just-mentioned H monkeys indicated that the H^+ monkeys were more impaired, thus implicating a role for the underlying cortex. Importantly, the

fact that the H^+ lesion nevertheless impaired memory less severely than the H^+A^+ lesion meant that anterior structures comprising the A^+ component of the large lesion must also be important.

The first clue about these anterior structures came from monkeys with stereotaxic lesions limited to the amygdala that spared surrounding cortex (Zola-Morgan et al., 1989a). These monkeys were fully intact on four memory tasks. Moreover, when the H^+ lesion was made conjointly with A lesions (the H^+A lesion), H^+A monkeys were impaired on the same four tasks but no more so than after H^+ lesions. These findings ruled out the amygdala and turned our attention to what else had been damaged when the amygdala was removed by the conventional surgical approach (the $^+$ component of the A^+ lesion).

As we began to consider what tissue subjacent to the amygdala might explain the considerable difference in the behavioral effects of H^+ lesions and H^+A^+ lesions, we realized that we didn't really understand the anatomy of the anterior medial temporal lobe. On a memorable Saturday evening (March 14, 1987), in one of our regular nightly phone calls, Stuart and I decided to cancel the surgery we had scheduled for the following Monday. Then on Monday, we took the brain sections from our earlier studies of H^+A^+ lesions over to David Amaral at the Salk Institute. He examined each of the slides and then said, "All these lesions have damage to perirhinal cortex." I remember throwing up my hands, saying, "That's it!"

Anatomical studies from David Amaral and his colleagues, published in the same year as our critical conversation with him, had indicated that the perirhinal cortex and the closely associated, and more posterior, parahippocampal cortex provide two-thirds of the cortical input to the entorhinal cortex. Given that the entorhinal cortex originates the major input to hippocampus, these two cortical regions thus provide the principal route by which information from the neocortex reaches the hippocampus. We therefore evaluated the severity of memory impairment in monkeys with lesions designed by David that were limited to the perirhinal cortex and parahippocampal cortex (the PRPH lesion) (Zola-Morgan et al., 1989b). The monkeys with PRPH lesions were severely impaired on three memory tasks, including DNMS, and overall, they were as impaired or more impaired than monkeys with the original H^+A^+ lesions. A later study of PRPH lesions showed the same severe deficit on the DNMS task in the tactual modality (Suzuki et al., 1993). Still later, lesions to perirhinal cortex itself, prepared by David, produced a modest, multimodal deficit on the DNMS task, as well as on two other memory tasks (Buffalo et al., 1999). Lesions of the immediately adjacent area TE, a major source of afferents to the perirhinal cortex, had entirely different effects that suggested a visual processing deficit, not a memory impairment.

With the results of the PRPH lesion in hand, we were ready to suppose that, if an H^+A lesion did not increase the impairment associated with an

H^+ lesion, then an H^{++} lesion should be effective, probably by virtue of damage to perirhinal cortex. We therefore prepared an H^+ lesion and brought it forward to include the cortex beneath the amygdala that typically had been included in the original H^+A^+ lesion. The H^{++} lesion severely impaired memory and approximated the effect of the large H^+A^+ lesion (Zola-Morgan et al., 1993). Quantitative measurement indicated that the perirhinal cortex was the only structure that was damaged more extensively in the H^{++} lesion than in the H^+ lesion.

Now we thought we had it, so we put together a paper identifying (announcing) the anatomical components of the medial temporal lobe memory system: the hippocampus, entorhinal cortex, and the adjacent, anatomically related perirhinal and parahippocampal cortices (Squire and Zola-Morgan, 1991). The amygdala, we wrote, is not a component of this system and has quite distinct functions (e.g., see Zola-Morgan et al., 1991). We emphasized further that this cortex along the parahippocampal gyrus is not simply a conduit for connecting neocortex to hippocampus. Both the H^{++} lesion and the PRPH lesion impaired memory much more severely than the H or H^+ lesion. Accordingly, the cortex damaged in the H^{++} and the PRPH lesions must be important for memory function on its own. Apparently, information from neocortex can reach the parahippocampal gyrus for some memory storage to occur and need not reach the hippocampus itself. We did not intend to imply that the structures of the medial temporal lobe therefore work together as a single and uniform functional unit, although this view sometimes has been attributed to us.

The monkey project, and the charting of the medial temporal lobe memory system, was one of the most satisfying pieces of work in my career, in no small part because of the pleasure of working with Stuart. It took a long time, but we knew the problem was solvable. Sustained collaboration between peers (we were only three years apart in age) is not so common in science, but it has many useful features. Everything is talked through so that it is hard to fool yourself. The thinking is out loud, as it were, and errors of logic, memory, interpretation, or emphasis are readily exposed.

Bringing in the Rats

Lesion-behavior studies in the monkey come with a number of challenges. Each animal is typically studied for one or two years with multiple tasks, and experiments must be carefully planned. Waste and inefficiency carry a high cost. Furthermore, studies requiring many animals, extended pilot work, or the charting of parametric effects are often out of bounds. So, in 1998, Stuart and I had discussions with Bob Clark, a postdoctoral fellow in our group, about the prospects of setting up a rat lab. The idea was to develop a program that would complement the monkey work and allow us to

pursue related questions. I had tended to view what I was studying as essentially mammalian, so it seemed reasonable to me that what we could learn from rats would be relevant to what we had been learning from monkeys and humans. Bob enthusiastically took this on, eventually obtained an independent faculty position, and collaborated with us (and then with me after Stuart left) on a number of useful studies until we retired the rat program in 2018.

As an example, it was well established in humans that immediate memory (the limited amount of information that can be held in mind such as a short string of digits), is intact after medial temporal lobe lesions and distinct from long-term memory, which is impaired. However, during the period that the animal model of human amnesia was being developed in the monkey, it was a matter of some debate whether the same distinction could be demonstrated in experimental animals. There was doubt if experimental animals even had an immediate (or short-term) memory and, if they did, perhaps it was organized differently than in humans.

In our study (Clark et al., 2001b), rats with hippocampal lesions first learned the DNMS task at a normal rate when the delay between the sample presentation and the choice was only 4 seconds. When the delay was then increased to 1 or 2 minutes, performance was impaired. Furthermore, during delayed testing, performance was intact when 4-second delay trials were introduced intermittently, indicating that both the nonmatching rule and short-term memory remained available. Most important, even when extended testing was given at a 1-minute delay, exceeding the training and testing that had been given at the 4-second delay, performance remained intact at the short delay and impaired at the long delay. This result demonstrated in the rat the same hippocampus-independent short-term memory and hippocampus-dependent long-term memory that we were familiar with in memory-impaired patients. Whether rats are actually holding short-term memory "in mind" is a different question.

Nicola Broadbent and Bob Clark also undertook a large study involving nearly 150 rats that helped explain why impaired performance on spatial memory tasks has been so easy to demonstrate after hippocampal lesions, and impaired recognition memory has often been difficult to demonstrate (Broadbent et al., 2004). Spatial memory deficits in the water maze were obtained after dorsal hippocampal lesions that encompassed only 30–50% of the total hippocampal volume, whereas object recognition was impaired only when the lesions encompassed 75–100% of the hippocampal volume. It appeared that spatial memory performance requires more hippocampal tissue than does recognition memory. Small hippocampal lesions that reliably impair spatial memory can spare recognition memory. Inasmuch as the water maze task is effectively a test of recall, I expect that one might find the same thing with any recall task, regardless of whether or not the task is spatial.

Another interesting issue emerged in the late 1990s when several animal studies suggested that the perirhinal cortex might be important not only for memory but also for visual perception, especially for discriminating between stimuli with high feature overlap. We carried out studies in patients, finding no evidence for this new view (Shrager et al., 2006; Kim et al., 2011; Knutson et al., 2013) but also wanted to construct a strong test of the idea in the rat. Using a two-choice discrimination task developed by Pamela Reinagel at UCSD, we first gave rats extensive training to discriminate between two pictures (paintbrush vs. flashlight). Rats then maintained memory performance at a high level while interpolated probe trials tested their perceptual ability (Clark et al., 2011). The probe trials varied the similarity between the two stimuli across 14 difficulty levels by gradually morphing one stimulus into the other. The 14 different probe trials yielded performance scores from 87% correct to chance (50% correct), and animals with perirhinal lesions and control animals obtained virtually identical scores at every difficulty level. Overall, we never found support for a role of perirhinal cortex in perception. We suggested, with others, that tests of this idea in animals tended to confound perception and memory because the tests used to assess perception typically require learning.

Lastly, we carried out a number of studies trying to understand why the temporal gradients of retrograde amnesia so commonly found in humans and animals, including in our rats (Clark et al., 2002a), had never been found in the water maze task. We made only a little progress on this problem, finding impaired (rather than spared) remote memory on three different versions of the water maze task, using training-surgery intervals as long as 14 weeks (Clark et al., 2005a), giving animals extensive water maze training early in life (Clark et al., 2005b), using reversible lesions (Broadbent et al., 2006), and using beacons to reduce the burden on navigation (Clark et al., 2007). It remains a puzzle to me, though we did offer some speculation about it based on limitations of rat frontal cortex and the performance requirements of the water maze (Clark et al., 2007; Kim et al., 2013b; Sapiurka et al., 2016).

I have supposed that these findings in the water maze are due to particular features of the task and need not imply that hippocampal lesions should generally impair remote spatial memory. First, a few studies by others have demonstrated spared remote memory after hippocampal lesions in other tasks that require some form of spatial memory (e.g., Tse et al., 2007, *Science*, *316*, 76–82). Second, a substantial study led by graduate student Edmond Teng is pertinent to this problem. Our patient E. P., despite his large medial temporal lobe lesions, could recall the spatial layout of the region where he grew up and then left as a young adult more than 50 years earlier (Teng and Squire, 1999). He also did it for PBS TV in the presence of the program's host, Alan Alda. He could mentally navigate, construct novel routes, and point correctly to landmarks while imagining himself at various locations. E. P. did all this as well as healthy controls who had grown up in the same

town and also moved away. Yet he had acquired no knowledge of the neighborhood where he had lived for six years after he became amnesic, and he could not point in the direction of the ocean, two miles away. We thought this was pretty strong evidence for sparing of remote spatial memory after hippocampal damage.

Multiple Memory Systems

Anyone with an interest in memory who lived through the 1960s and 1970s remembers the confusion that abounded as investigators tried to replicate patient H. M.'s memory impairment in rats and monkeys. Animals with lesions similar to H. M.'s 1953 lesion, even monkeys prepared by H. M.'s surgeon, did not exhibit what one would call a memory impairment. It took Mishkin's demonstration in monkeys of a memory impairment in the DNMS task (in 1978) to show that a viable animal model of H. M. might be within sight. Why it took so long is a fascinating story.

The story begins with Brenda Milner's discovery in 1962 that H. M., despite the severity and scope of his memory impairment, was capable of learning a hand-eye coordination skill (mirror drawing) over a three-day period, although on each day, he had no memory of having practiced the task before. While this showed that H. M.'s memory impairment was not absolute, discussions for a long time afterward tended to set motor skills aside as an exception, a less cognitive form of memory, with the view that all the rest of memory was of one piece and was impaired in amnesia. Yet, it turned out that motor skills were just the beginning.

My first graduate student, Neal Cohen, and I had the good fortune to find the first hint of what lie beyond motor skills when we considered that certain pattern-analyzing abilities seemed to share some properties with motor skills. We discovered that memory-impaired patients could acquire the perceptual skill of reading mirror-reversed words at a normal rate, despite poor memory for the task and for the words that had been read (Cohen and Squire, 1980). The finding suggested to us a principled distinction between the learning of procedures and the remembering of facts, reminiscent of the philosopher Gilbert Ryle's 1949 distinction between "knowing how" and "knowing that." Neal took all this across campus to consult with David Rumelhart, a gifted cognitive scientist, and returned with news of a distinction between declarative and procedural knowledge, which had been introduced recently in the literature of artificial intelligence. The distinction apparently had not gained much traction there, being seen rather as two different, equally useful, ways to represent information. But it seemed exactly right to us as a brain-based distinction describing what we thought to be a fundamental idea about the organization of memory. Our idea was that declarative memory is available as explicit recollection and is impaired in amnesia. Procedural memory is skill-based information embedded in

procedures that can be expressed only through performance, that is, by executing the procedures. Procedural memory is spared in amnesia.

We soon found other examples of preserved learning, some of which seemed to move beyond skill learning itself: the ability to resolve stereoscopic images; effects of recent context on perceptual judgments, termed adaptation-level effects (Benzing and Squire, 1989); cognitive skill learning (Squire and Frambach, 1990); text-specific reading skill (Musen et al., 1990); artificial grammar learning (Knowlton et al., 1992); and category learning (Knowlton and Squire, 1993). Still other examples, studied by us and others in the 1980s, came from the phenomenon of priming and from classical conditioning (see later sections), and took us even further beyond skill learning. Indeed, the diversity of phenomena found to be spared in amnesia soon persuaded us to set aside the declarative-procedural terminology in favor of a biological distinction between declarative and nondeclarative memory (Squire and Zola-Morgan, 1988). Declarative memory is dependent on the medial temporal lobe, and nondeclarative memory is an umbrella term referring to multiple kinds of memory supported variously by the neostriatum, amygdala, cerebellum, and neocortex. At about that time, I began using a tree diagram rather than a dichotomy to represent the memory systems of the brain (e.g., Squire, 1986). Endel Tulving also wrote about multiple memory systems during this period from a psychological perspective (1985, *American Psychologist*, *40*, 385–398). What had happened in the early 1980s was the discovery that memory impairment after hippocampal lesions is a much narrower condition than originally thought. Some tasks that had been given to animals with lesions, in efforts to model H. M.'s memory impairment, were tasks that animals could learn nondeclaratively. In other words, the objective of replicating H. M.'s memory impairment in animals was for many years defeated because there was not yet an accurate description of the condition that needed to be modeled.

Another interesting task, different from a skill, is the gradual feedback-guided learning that results in habit learning. Following on work by others in rats and monkeys, which had suggested the importance of the neostriatum (not the hippocampus) for habit learning, we asked whether there was a parallel in humans to this kind of learning. We tested memory-impaired patients and patients with Parkinson's disease on a probabilistic classification task (the weather task). In this study, led by postdoctoral fellow Barbara Knowlton, participants tried to learn which of two outcomes (rain or sunshine) would occur on each trial (Knowlton et al., 1996). Each of four cues was probabilistically related to the outcome, and on each trial one, two, or three of the cues was presented. The idea was to defeat the strong tendency to memorize cue-response associations (using declarative memory) and to encourage decisions based more on a gut feeling. Memory-impaired patients learned the task but later could not answer questions about the training episode. Patients with Parkinson's disease failed to learn

the task but had intact memory about the training. This double dissociation of lesion and task demonstrated that the brain areas damaged in the two patient groups, the neostriatum (caudate and putamen) and the medial temporal lobe, supported separate and parallel learning systems. The findings further demonstrated that habit learning tasks in humans could be acquired nondeclaratively.

Characteristics of Declarative and Nondeclarative Memory

During this period, we were sometimes asked whether declarative and nondeclarative memory differed in any interesting way other than that declarative memory was impaired by medial temporal lobe lesions and nondeclarative memory was not. One would expect that if the distinction were biologically important, different kinds of memory should have different purposes and different operating characteristics. An insight into this issue came when Paul Reber, a postdoctoral fellow, used transfer tests to assess what participants knew about the weather task after successfully learning it. The transfer tests either created new conditions that required flexible use of task knowledge or simply recreated the conditions of the training task (Reber et al., 1996). Controls exhibited flexible knowledge, but the memory-impaired patients did not. This result suggested that one difference between declarative and nondeclarative memory is the difference between flexibly organized information and rigidly organized, inflexible information.

We encountered a more dramatic example of this when we tried to teach our patient E. P. a series of 48 three-word sentence frames (e.g., MEDICINE cured HICCUPS) during 24 study sessions given over a period of 12 weeks (Bayley and Squire, 2002). E. P. performed much more poorly than controls, but eventually achieved a score of 18.8% correct on retention tests given after 24 sessions (MEDICINE cured ???). Controls scored 49.5% correct after only two study sessions. We had thought that E. P. might simply have some residual ability for acquiring declarative memory. Yet, what E. P. learned was different from what controls learned. What E. P. learned proved to be inflexible and available only when the original training conditions were reinstated. When the middle word of the sentence was replaced by a synonym (e.g., MEDICINE relieved ???), his performance collapsed altogether, and he answered only one question correctly. This same manipulation scarcely affected control performance. It was also striking that E. P. was entirely unaware of the little that he had learned. His confidence ratings were the same for correct and incorrect responses, he did not acknowledge that he was sometimes producing correct answers, and he never gave an indication that the test material was familiar.

Based on this result, together with what we had been finding with priming and classical conditioning (see later sections), we had begun to suppose that awareness of what was learned might be another key feature

of declarative memory and that performance on medial temporal lobe-dependent tasks reflects aware (conscious) memory. Conversely, performance on medial temporal lobe-independent tasks reflects unaware (unconscious) memory. This formulation was frequently challenged based on indications that some hippocampus-dependent tasks appeared to be acquired in the absence of awareness. Also, many preferred the idea that the nature of the task, rather than the presence or absence of conscious knowledge, determined whether learning depends on the medial temporal lobe. We looked into all these proposals rather carefully, through experiment, and always found additional support for our original formulation. For example, in tasks of transitive inference, participants were first trained on overlapping pairs of items (e.g., A+ B-, B+ C-, C+ D-, D+ E-, where + and - indicate correct and incorrect choices). Later, participants who chose B over D when presented with B and D were said to demonstrate transitive inference. Christine Smith found that the ability of healthy volunteers to exhibit transitive inference was directly related to their awareness of the hierarchical relationship among the training elements (Smith and Squire, 2005). Patients with hippocampal damage were unaware of the hierarchy and did not exhibit transitive inference.

In other studies, we were able to construct critical tests of the connection between aware learning and hippocampal function when memory was assessed by eye movements. As first shown by Neal Cohen and his colleagues, individuals tend to inspect novel scenes differently than familiar scenes, and they tend to direct their gaze disproportionally toward a region of a scene that has been altered. In our work, led by Christine Smith, we consistently found that the tendency to gaze at the manipulated region of a scene occurred only when individuals were fully aware that a manipulation had occurred (Smith et al., 2006; Smith and Squire, 2008). Memory-impaired patients, overall, did not direct their gaze toward the altered region because they usually did not remember the scenes. But, on a few occasions, when they were aware of the manipulation, they (like controls) gazed at the altered region (Smith and Squire, 2018). We found the same link between conscious memory and medial temporal lobe function when eye movements were recorded as individuals tried to decide which of three scenes they had recently studied (Urgolites et al., 2018).

In another study, we found the other kind of link: an eye movement effect that was independent of conscious knowledge and that was also independent of the medial temporal lobe (Smith and Squire, 2017). Healthy controls explored new and old scenes differently (making fewer fixations and sampling fewer regions when looking at old scenes), but this effect was unrelated to whether they correctly recognized each scene's new-old status. Moreover, memory-impaired patients exhibited the same differential exploration of new and old scenes as controls. Thus, our data remained consistent with the idea that declarative memory represents flexible, conscious

knowledge and is dependent on the medial temporal lobe. When performance is unrelated to and independent of conscious knowledge, as in the latter study, performance is independent of the medial temporal lobe.

The Concurrent Discrimination Task

Perhaps the most compelling demonstration of the characteristics of declarative and nondeclarative memory came from a different direction, when we were forced to reexamine the eight-pair concurrent discrimination task. This task, which had been used for years in work with monkeys, involves learning which object in each of the eight object pairs has been designated "correct." Typically, 40 trials are presented each day, one pair at a time, such that each pair is encountered five times. For humans, this is a typical declarative memory task. Participants memorize which object is correct in each pair, and they can learn in two or three sessions. Patients with medial temporal lobe lesions were markedly impaired on this task (Squire et al., 1988).

One day in the mid-1990s, our graduate student, Beth Buffalo, came to the lab meeting with the records for all the monkeys in our lab that had ever been tested on the concurrent discrimination task. Normal monkeys learn this task in about 500 trials. Beth told us that monkeys were impaired on the task, not by the medial temporal lobe damage itself, but only when the lesion reached laterally enough to include visual area TE (Buffalo et al., 1998). Subsequently, Ed Teng found an impairment in the concurrent discrimination task when the lesion included the tail of the caudate nucleus (Teng et al., 2000). This was pretty surprising news, because in our big 1983 review, Stuart and I had endorsed the concurrent discrimination task as one of three tasks appropriate for modeling H. M.'s impairment in the monkey. Yet now, with these new findings, and remembering the weather task and the nature of habit learning, we had to suppose that monkeys were likely learning the concurrent discrimination task as a habit. The critical anatomical projection then would be, not from visual area TE to the medial temporal lobe, but from area TE to the caudate nucleus. If so, the implication would be that humans and monkeys were learning the same concurrent discrimination task with different brain systems.

This idea raised a fascinating question. Might patients with profound amnesia, and no apparent capacity for declarative memory, be able to learn the concurrent discrimination task as the monkey learns it, not rapidly as declarative memory but slowly as a habit through gradual trial-and-error learning? If so, would the patients then acquire unconscious knowledge (whatever that might mean for this task) and would this knowledge have different properties than if it had been learned declaratively? We tested two patients with large medial temporal lobe lesions, E. P. and G. P., twice each week by presenting each object pair and asking them to make a choice by

picking up one of the objects, turning it over, and discovering whether the word "correct" appeared beneath the object's base (Bayley et al., 2005a). Controls mastered the task in three sessions. Surprisingly, E. P. and G. P. learned successfully as well, but only gradually during the 36 and 28 sessions, respectively. They eventually reached a score of 95% correct after more than 1,000 trials. Yet, in interviews before each testing session, they never could describe the task, the instructions, or the objects. Even during testing, they never recognized that they had encountered the task before. Comments offered by the patients during the test days were particularly illuminating. When asked after session 34 if he had a strategy, E. P. said, "No. It's just up here [pointing to head] . . . It seems like it's up there, and it comes down and out." When asked during session 23, "Why are you selecting that one?" G. P. said, "It's just jumping out at me 'I'm the one.' I keep wanting to pick it."

To test if the acquired knowledge were rigidly organized, as we thought it should be in the case of nondeclarative memory, we administered a sorting task a few days after training was complete. All 16 objects were put together, and participants were asked to sort them by placing the correct objects to one side and the incorrect objects to the other side. Controls had no difficulty (95% correct). E. P. and G. P. failed altogether (56% and 50% correct, respectively). E. P. placed nine objects in one group and seven in the other. When he moved to look underneath one of the objects and was stopped by the examiner, he said, "That's just a habit I think. It's just, what's underneath?" So here was a particularly useful example from the domain of habit learning of the distinction between conscious (declarative) and unconscious (nondeclarative) learning systems. For controls, the learning was rapid and resulted in a capacity for flexible use of conscious knowledge. For the patients, the learning was slow and resulted in unconscious, rigidly organized information that was unavailable when testing was conducted in a novel way.

Priming

Priming is a form of nondeclarative memory distinct from skill and habit learning. It is evident as improved access (measured by speed or accuracy) to recently presented items, such as words, objects, or even illegal nonwords (Hamann and Squire, 1997b). Priming was fascinating to me because it occurs entirely outside of awareness. The phenomenon is everywhere, but it is a phenomenon of perception, not an experience of memory. In a splendid review of priming's early years, Tulving and Schacter remarked, "It is difficult to study phenomena whose existence one does not suspect" (1990, *Science*, *247*, 301–306). An early antecedent used methods that we now know can demonstrate priming (Warrington and Weiskrantz, 1970, *Nature*, *228*, 628–630). Memory-impaired patients exhibited near-normal

performance when three-letter word stems (MOT__) were given as cues for recently presented words (MOTEL). Yet, we and others trying to use the same methods often found impaired (not spared) performance (e.g., Squire et al., 1978).

Motor skills, perceptual skills like mirror reading, and habit learning were different, I thought. These develop gradually over many trials, and I was doubtful that patients could perform at an intact level on any test based on single items. I was wrong but eventually made sense of it when we discovered the crucial role of the instructions in determining how individuals approach the task. With standard memory instructions (use this three-letter cue to help you recall a recently presented word), controls showed the expected advantage over patients (Graf et al., 1984). That is, the controls identified more of the study words than did the patients. However, when the instructions were changed so as to discourage a declarative memory strategy (use this three-letter word stem to form the first word that comes to mind), the results were different. Memory-impaired patients now exhibited consistently intact performance, completing word stems to form study words at the same rate as controls.

Priming can last a long time. In one experiment, memory-impaired patients and controls named objects and then two or seven days later named the same objects about 100 msec faster than other objects that had not been presented earlier (Cave and Squire, 1992). This effect occurred despite the fact that the patients were severely impaired at remembering the objects themselves. Another notable feature of priming is that it is diminished by manipulations that scarcely affect declarative memory, such as changing the size or shading of an object that was presented earlier, changing from one object to a different object with the same name (Cave and Squire, 1992), or changing the modality of item presentation (Graf et al., 1985). Thus, priming proved to have the same rigid, inflexible kind of organization that was found in other forms of nondeclarative memory. Priming is presumably advantageous because animals evolved in a world where things that are encountered once are likely to be encountered again.

For many years, a popular idea was that priming provides information that individuals can use to make conscious judgments of familiarity. The idea was that a recently presented item (a word, for example) would "pop out" when encountered later and that this would help with deciding whether the word had been presented earlier. Some proposed that the operation of priming could explain why amnesic patients typically perform a little better than chance (50%) on recognition memory tests for novel and familiar items. Yet it seemed to me that priming usually goes unnoticed. One is not aware that a recently studied object is later named more quickly, and one is often unaware even that the "first word to come to mind" in a word-stem completion task was actually a word from a recent study list.

Initially, we found a way to test whether priming benefitted recognition memory in patients receiving ECT. At an early time after treatment (45 minutes), priming was fully intact, but patients still performed at chance on the memory tests (Squire et al., 1985). Later, we tested the idea in multiple ways with patient E. P. E. P.'s memory impairment was so severe that he consistently performed at chance on recognition memory tests. Yet, he exhibited fully intact perceptual and conceptual priming (Hamann and Squire, 1997a; Levy et al., 2004). In one case, he even performed at chance on the recognition memory test when he was given access to his intact priming response just before the recognition test (Stark and Squire, 2000b). These findings ruled out the idea that recognition judgments of familiarity receive any measurable benefit from the operation of priming, and they emphasized the independence of priming and declarative memory. We subsequently showed directly that priming provides only a weak and unreliable cue about prior occurrence (Conroy et al., 2005).

Some information about the neural substrates of priming came when I had the chance to collaborate with Marc Raichle, Steve Petersen, and others in St. Louis in what turned out to be the first functional neuroimaging study of memory (Squire et al., 1992). The memory condition itself activated the hippocampal region. Priming was associated with a reduction of activity in right posterior visual cortex in the region of the lingual gyrus. It appeared that, following presentation of a stimulus, less neural activity is needed to process the same stimulus again. One possibility is that the second presentation of a stimulus leads to a net reduction in activity together with a sharpened response to the repeated stimulus. In any case, the evidence pointed to independent brain systems supporting priming and declarative memory. Visual priming occurs within perceptual processing systems, where changes occur well before information reaches the medial temporal lobe and visual perception is transformed into visual memory.

Classical Eyeblink Conditioning

In the context of the distinction between conscious (hippocampus-dependent) and unconscious (hippocampus-independent) memory systems, I had always been curious about trace conditioning. Trace conditioning is a variant of classical conditioning. In the case of trace eyeblink conditioning, the conditioned stimulus (CS), such as a tone, is presented and terminated, followed by a short interval of a few hundred milliseconds before presentation of an air puff, the unconditioned stimulus (US). Initially, the US elicits an eyeblink, but with repeated CS-US pairings, the CS elicits a conditioned eyeblink response (CR) in advance of the US. Trace conditioning was known to require the hippocampus. Yet, the trace interval is so short that one would not expect it to cause any difficulty for memory-impaired patients. Even severely impaired patients, such as H. M. and E. P., can easily hold onto

information for many seconds. So, why should trace conditioning require the hippocampus?

Bob Clark in the lab had worked with eyeblink conditioning in graduate school (albeit with rabbits) and was interested in the problem. We started with the idea that trace conditioning in humans might require some kind of long-term declarative memory, perhaps knowledge (awareness) about the CS-US relationship across many trials. In our first study, patients with medial temporal lobe damage, including E. P., received differential conditioning with two CSs (a tone and white noise), such that one CS was always paired with the US (CS^+) and a second CS was always presented alone (CS^-) (Clark and Squire, 1998). We compared differential trace eyeblink conditioning with differential delay eyeblink conditioning. For delay conditioning, the CS^+ was presented a few hundred milliseconds before the US, and the two stimuli coterminated. Delay conditioning was known to be independent of the hippocampus. We also asked a number of questions after conditioning to assess how much knowledge participants had acquired about the temporal relationship between the CS and US (i.e., that the CS predicted the US). The finding was that the patients acquired delay conditioning at a normal rate but failed to acquire trace conditioning. Patients did not learn about the relationship between the CS and US during either kind of conditioning. Controls who did not learn about the CS-US association still acquired delay conditioning but did not acquire trace conditioning. Thus, awareness of the CS-US relationship was irrelevant for delay conditioning but was essential for trace conditioning.

Some suggested that the extra demands of differential trace conditioning (processing two CSs and appreciating their different relationship to the US) might require awareness, whereas the same requirement might not hold for the simpler, single-cue conditioning procedure. Yet, we found the same thing with single-cue conditioning. In a series of experiments, led by Joe Manns in collaboration with Bob Clark, volunteers received 120 trials of CS-US pairings with either single-cue trace conditioning or single-cue delay conditioning. For single-cue trace conditioning, the awareness score achieved after 10 trials correlated significantly (+0.49) with the strength of conditioning (percent CRs) across all 120 trials. In contrast, for single-cue delay conditioning, the correlation was not significant (-0.13) (Manns et al., 2001; see also Manns et al., 2002). Other work emphasized that delay and trace conditioning are fundamentally different phenomena (Clark et al., 2001a). For delay conditioning, CRs were closely related to the strength of the CS-US association. For trace conditioning, CRs were related to expectation of the US, that is, to knowledge that the US would occur.

In an additional study of differential trace conditioning, we tracked the development of knowledge about the CS-US relationship by asking one group to predict on each trial whether the US would occur, and asking a second group of participants whether they would blink (Manns et al., 2000).

Asking participants to predict their eyeblinks inhibited the acquisition of awareness about the CS-US relationship as well as the acquisition of trace eyeblink conditioning. In contrast, asking participants to predict the onset of the US promoted both awareness of the CS-US relationship and trace conditioning. Acquisition of knowledge about US onset and acquisition of trace conditioning itself developed concurrently.

This set of studies showed us that the development of awareness (the CS predicts the US) is an essential feature of successful, trace eyeblink conditioning. Awareness did not directly drive the eyeblinks. Indeed, participants typically did not become aware of their eyeblinks or that they were blinking in response to the CS. Yet, awareness of what was being learned (the relationship between CS and US) accompanied trace conditioning, just as in the typical declarative memory task where, if learning is to succeed, participants acquire conscious knowledge of what they are learning (memorizing word pairs, memorizing a route, and so on).

Trace conditioning, like delay conditioning, depends on the cerebellum. Importantly, trace conditioning also depends on the hippocampus and medial prefrontal cortex. We suggested that trace conditioning requires the acquisition of declarative memory because the trace interval (which can be as long as 1000 msec) makes it difficult for the cerebellum to process the CS-US relationship in an automatic, reflexive way (Clark et al., 2002b). Electrophysiological studies have not detected activity in the cerebellum for longer than 100–200 msec following the termination of a single input pulse. However, if the hippocampus and neocortex have represented the stimulus contingencies, then information about the CS and US might be available to the cerebellum in a format it can use (i.e., just before and during the US). Our idea was that awareness during conditioning is a marker, or indicator, that the hippocampus and neocortex are effectively engaged by the task. Awareness is an emergent property of their operation. We also could not resist suggesting that hippocampus-dependent learning in nonhuman animals may be accompanied by some form of awareness.

Recollection and Familiarity

The long-standing distinction between recollection and familiarity refers to two ways in which an item can be recognized as having been presented before. Recollection involves remembering specific contextual details about the episode in which an item was encountered, and familiarity involves simply knowing that an item was presented. I had become interested in this distinction in the course of extended conversations with John Wixted that struck up in the early 2000s. John is professor of psychology at UCSD, accomplished in the cognitive science of memory, and a rigorous scholar. The conversations eventually led to collaboration, and working with John has been one of the pleasures of the more recent part of my career.

At the time, John and I began talking, there was broad interest in how the different structures of the medial temporal lobe contributed to declarative memory, and out of this climate came the proposal that recollection depends on the hippocampus and familiarity on the adjacent perirhinal cortex (Brown and Aggleton, 2001, *Nature Reviews Neuroscience*, *2*, 51–61). John pointed out that studies appearing to support the idea usually involved a comparison between strong, recollection-based memories and weak, familiarity-based memories (Wixted and Squire, 2011). That is, most studies confounded memory strength with recollection and familiarity. I had my own reservations because I was not seeing signs of this distinction in the behavior of our hippocampal patients. They did not express familiarity with test material, while missing only source memory ("where" and "when") or other details about previous episodes. They simply reported that material was not familiar. In addition, when Jeri Janowsky was in the lab as a postdoctoral fellow and set up a small group of frontal lobe patients, the frontal patients were not amnesic, but they made source memory errors—such as misidentifying where they had acquired information (Janowsky et al., 1989). Source memory errors are errors of recollection. It seemed to me that, whereas the recollection-familiarity distinction might not illuminate hippocampal function, it might be relevant to frontal cortex.

We began discussing how to bring the matter to experiment, drawing on work by Craig Stark in the lab about the construction of fMRI studies and the optimal design of baseline conditions (Stark and Squire, 2000a, 2001). Our approach went in a number of directions, and most of the good ideas were John's. In one project, led by postdoctoral fellow Brock Kirwan, we designed an fMRI study such that item memory strength and source memory strength could be assessed independently (Kirwan et al., 2008b). Measuring item memory strength independently of source memory (recollection) was intended to measure the strength of familiarity-based memory. Volunteers saw 360 nouns in the scanner, making animate/inanimate judgments when the nouns were presented in green and size judgments (smaller than a shoebox?) when the nouns were presented in red. Subsequently, in a memory test outside the scanner with the 360 old words and 360 new words, participants made recognition decisions (the item-memory question) on a 6-point confidence scale (1, sure new to 6, sure old). Confidence ratings provide a measure of item memory strength. For words judged old, they also made a source memory decision on a 6-point confidence scale about which judgment had been made when the word was studied earlier (1, sure animacy to 6, sure size).

The first analysis was planned to identify brain regions in which the activity at study varied linearly as a function of subsequent item-memory strength, while holding source memory strength constant at chance levels. To do this, we included in the analysis only trials in which items judged old (ratings of 4, 5, or 6) were associated with the lowest possible source

confidence (ratings of 3 or 4). Because recollective success (i.e., source memory) was weak and invariant in this analysis, any findings would most likely be related to the success of familiarity-based memory. In this analysis, activity in both the hippocampus and perirhinal cortex predicted subsequent memory strength. Next, we found regions in prefrontal cortex where activity at study varied linearly as a function of subsequent source-memory strength, while item-memory strength was held constant at a high level. In this case, the analysis was limited to correct item judgments with a confidence rating of 6. The absence of a hippocampal finding in this analysis suggested to us that hippocampal activity, when it occurred, was indicative of strong memories rather than recollection *per se* (Kirwan et al., 2008b). Indeed, other work confirmed that memory strength must be strong before elevated fMRI activity can be observed in the hippocampus (Song et al., 2011c).

Although I found this study particularly compelling, a single study doesn't always do much to correct a large idea. It is better, I think, to find additional ways to test an idea and to be hit over the head with the data rather than to have to help it along with argument. In the end, we found a number of useful ways to explore the issue, and the topic was with us from my first collaboration with John (Wais et al., 2006) through a novel study developed by graduate student Adam Dede (Dede et al., 2014). Four postdoctoral fellows and three graduate students made significant contributions to 12 research articles, reporting the results of 12 different experimental attacks on the problem (notably, Kirwan et al., 2010; Smith et al., 2011; Song et al., 2011a; Song et al., 2011b; Dede et al., 2013). The memory-strength confound, as we called it, had led many astray. Recognition memory decisions associated with recollection usually reflect stronger memory than recognition decisions associated with familiarity. But recollection can be weak, and familiarity can be strong. When one matches the strength of these two constructs, one finds hippocampal activity in fMRI associated with both recollection and familiarity (Smith et al., 2011).

We ended up with the perspective that hippocampal activity during learning predicts subsequent memory strength, regardless of whether memory is based on familiarity or recollection, whereas activity in prefrontal cortex predicts the success of recollection. Some took this idea to mean that the hippocampus is important only when memory is strong. However, we meant only that memory must be strong to detect hippocampal activity in fMRI, not that the hippocampus plays no role in weak memory.

It was a pretty comprehensive body of work, and our experiments seemed to persuade not a few people. A count of publications in six major neuroscience journals each year that used the terms recollection and familiarity shows a peak of 135 in 2010-2013 but only 24 in 2017-2020. Meanwhile, how medial temporal lobe structures might contribute differently to declarative memory remains a topic of interest. Our view is that the matter will be best

informed by findings from neuroanatomy and neurophysiology and that different structures will prove to support different attributes of memory (e.g., visual, auditory, spatial) (Wixted and Squire, 2011).

Memory and Spatial Cognition

For decades now, anyone taking up the study of hippocampal function knows that he or she has taken up a problem guided by two different, and potentially conflicting, traditions of work. One tradition began in 1957 with the description of patient H. M. and emphasizes the role of the hippocampus in memory function. The other tradition began in 1971 with the discovery of place cells in rodents. This tradition does not deny the importance of memory but also identifies a role for the hippocampus in spatial navigation and spatial cognition. There has been much discussion whether and to what extent these two accounts are compatible. One suggestion, which has much to recommend it, is that one account can simply be folded into the other (see "The Role of the Hippocampus in Navigation Is Memory"; Eichenbaum, 2017, *Journal of Neurophysiology, 117,* 1785–1796).

But not all of the second tradition can be accommodated in this way, and for a long time, I have thought that the two accounts lead to a contradiction. The contradiction arises because a key finding from the memory tradition was that short-term (working) memory is independent of the hippocampus and fully intact in patients such as H. M. Patients (or rats) with hippocampal lesions should therefore be able to perform all manner of tasks, including spatial tasks, so long as a task can be managed within working memory (i.e., by actively maintaining task information in mind). In contrast, some accounts coming from the spatial tradition hold that the hippocampus carries out computations needed for navigating, for locating oneself in space, and for internally constructing spatially coherent scenes. In this view, patients such as H. M. should fail spatial tasks that call on these abilities, even when task performance can be supported by working memory or when a task scarcely requires memory at all.

These ideas don't directly mandate which tasks are most suitable for deciding between the two perspectives. However, it is possible to present simple tasks that require participants to construct and operate on spatially coherent mental images and that place little burden on memory. For example, we gave hippocampal patients four tasks assessing the capacity for spatial mental imagery (Kim et al., 2013a). One task asked 108 true/false questions, such as: "Between 7 and 9 o'clock, the tip of a clock's hour hand moves to the left." Answering this question requires constructing a coherent mental image and making a judgment, but it does not require memory beyond the ability to hold a mental image in mind for a few seconds. The patients performed as well as controls on all four tasks, though as expected, they had difficulty afterward remembering the test materials. In another

study, patients did as well as controls at imagining and describing what might lie beyond photographs of scenes that they viewed, and they also used as many spatial referents in their narratives as did controls (Kim et al., 2015). In another task from this same study, patients exhibited the phenomenon of boundary extension, the normal tendency to draw a simple scene immediately after viewing it, such that the scene has a larger background than was actually presented.

In still other spatial tasks, hippocampal patients were fully intact at navigating with hand-held maps (Urgolites et al., 2016), matching spatial layouts to identical layouts presented from a different viewpoint (Urgolites et al., 2017), recognizing scenes after shifts in viewpoint (Rungratsameetaweemana and Squire, 2018), and making possible/impossible judgments about the structural coherence of three-dimensional scenes (Urgolites et al., 2019). In two additional studies, hippocampal patients produced as many details as controls as they tried to imagine plausible future episodes, and they included in their narratives as many spatial details as did controls (Squire et al., 2010; Dede et al., 2016b).

Lastly, valuable information came from a new task developed by Adam Dede. Patients with hippocampal lesions or large medial temporal lobe lesions took a 25-minute guided walk during which 11 planned events occurred. Then, immediately afterward, they narrated what they could remember about the events of the walk (Dede et al., 2016a; Heyworth and Squire, 2019). As expected, the patients remembered many fewer details about the walk than did controls, and they recalled about as much as controls tested 2.6 years after the walk. Nevertheless, patients reported details that had the characteristics of episodic recollection. The pertinent finding was that the patients had no particular difficulty recalling spatial details in comparison to other kinds of details, despite the need to construct spatially coherent images if one is to recollect spatial content. What we found instead of spatial problems were problems with temporal organization. Unlike controls, who tended to recall the events of the walk in chronological order, even after 2.6 years, the patients recalled the events in a haphazard order that had no relationship to the order in which events actually occurred.

Across all these tasks, from mental imagery to episodic recollection, we found no examples of spatial deficits in patients with hippocampal lesions. When we turned to tests of path integration, however, we found something different in rats. Path integration refers to the ability to use self-motion cues as one moves through space to keep track of a reference location. In the study, rats or humans entered a circular arena, searched for a target, and then tried to return to the start location (Kim et al., 2013b). Patients with hippocampal lesions, even patient G. P. with large medial temporal lobe lesions, were fully intact at path integration, presumably as a result of using working memory to hold the start location in mind while searching for the target. The surprise was that rats with hippocampal lesions failed

altogether. We were particularly interested in trials that were accomplished quickly, because those trials should afford the best chance for working memory to support performance. Yet, rats could not find their way back to the start location even in the most favorable conditions, when the outward path was less than 1 meter long, when they traveled in a straight line to find the target, and when the target was found within 3 seconds.

Although this result seemed to give weight to the idea that the rat hippocampus supports certain spatial functions, there may be a different way to think about it. Inasmuch as patients appeared to succeed at path integration by relying on an intact working memory, might rats have failed because their capacity for working memory was inadequate for this task? That is, perhaps rats are limited, in comparison to humans, in their ability to construct a coherent working memory of spatial environments. Could the difficulty then lie in limitations of rodent frontal cortex rather than in an impaired spatial function dependent on the hippocampus? More needs to be done on this large topic, but to my mind, evidence from many sources has been moving the discipline toward a broader view that affords the hippocampus and its place cells a role in representing both spatial and nonspatial information that can then be used for the formation of long-term memory (e.g., Buffalo, 2015, *Hippocampus*, *25*, 713–718; Aronov et al., 2017, *Nature, 543,* 719–722).

A challenge of this kind of work in memory-impaired patients is that only small numbers of patients are typically available to any one laboratory, different methods have been used to determine the locus and extent of neuropathology, and the etiology of the hippocampal damage can vary. In some cases, there has been insufficient attention to neuroanatomy and the likelihood of damage in addition to the hippocampus. I am skeptical that the modest impairments reported by others in a few of the spatial tasks described earlier were due to hippocampal damage itself. For example, can one attribute to hippocampal damage the finding of a modest impairment in three-dimensional scene perception in patients who have less extensive hippocampal damage than our patients and less severe memory impairment as measured by the same memory tests (McCormick et al., 2017, *Hippocampus*, *27*, 303–314; compare with our finding of intact three-dimensional scene perception in Urgolites et al., 2019)? I have been known to claim that, after a year spent with a hippocampal patient, a report of one's impressions would not include the word "spatial."

Other Kinds of Memory Impairment

I sometimes get calls from patients, family members, attorneys, or journalists about memory impairment. More often than not, the calls are about what I call "the other kind of amnesia," functional amnesia, which belongs to the realm of psychiatry rather than neurology. Most published reports

are single-case studies. My neurological colleague, Mark Kritchevsky, and I were able to carry out the first neuropsychological study of a series of such patients (n = 10; Kritchevsky et al., 2004). All patients remembered day-to-day events after the onset of amnesia, although some performed poorly on tests of verbal learning. The main finding was substantial loss of past autobiographical memory and a variable pattern of sparing and loss on tests of past public events and famous faces. All patients had a significant premorbid psychiatric history and eight still had retrograde amnesia for personal memories at last contact (median = 14 months after onset). The variability in findings, we suggested, was related to differences between patients in their commonsense concepts about memory and how it works.

Certainly the most unusual call came from the husband of a woman who, since a minor car accident in 2005, had been unable to remember events from one day to the next. Each day, her memories accumulated for the events of that day but then disappeared during each night of sleep. To our knowledge, this presentation was unique to the medical literature, but it had been depicted in the fictional film *50 First Dates* (2004). On testing, she demonstrated no memory at all for material she knew had been presented the day before (Smith et al., 2010). However, when testing included some of yesterday's material, covertly sprinkled in with other material learned earlier on the same day, her memory was good for all of it. Subsequently, she was "cured" after our referral to Paul McHugh at Johns Hopkins, where it was suggested that she interrupt her sleep at 4-hour intervals. The idea was that she could interpret these rests as "naps" and not the full night of sleep that she thought was the cause of her forgetting. Since her case was published, we have received four communications from around the world describing a similar condition. Those who have worked with such patients, including us, have not believed that the patients were consciously simulating their condition. At the same time, it is not well understood when or how or to what degree behavior can be organized and controlled unconsciously.

Final Threads

I am fortunate to have been able to work in the world of science, to have received sustained funding from NIMH (my RO1 is currently in years 42 to 46), to have had funding from the Department of Veterans Affairs for just as long, and to have published in seven calendar decades. I am especially grateful for the support of the late Lewis Judd, long-time chair of the Department of Psychiatry here at UCSD where I have my primary academic appointment. I am also grateful for the support of Gerhard Schulteis, associate chief of staff for research at the VA San Diego Healthcare System where I am appointed as research career scientist.

The work that has been done has depended on the energy of many undergraduate volunteers and research assistants, and on the dedication

and talents of 17 graduate students and 24 postdoctoral fellows who are acknowledged by citation in the preceding pages and in the list at the end. But students and postdocs are not enough for work with patients. One can't send out a stream of trainees to patient homes. The whole operation depends on a senior staff person who can nurture long-term, social worker-like relationships with the patients and their families, do the testing, supervise other research assistants, and work with the students and postdocs. In this role, there was Joyce Zouzounis (20 years) and now Jennifer Frascino (since 1997). Jennifer is research coordinator, tester, supervisor, and collaborator. She is beyond extraordinary, and I am lucky and grateful to have her with us. An administrative assistant was always essential to the lab as well, and I mention two who were long-serving and appreciated by all of us (Lilian Fontana, 12 years, and Sherry Hargrove, 14 years). In 2018, lab members organized a Fest in the form of a symposium and reunion of colleagues, trainees, and staff from around the world.

I am also grateful for the inspiration of three colleagues in the generation ahead of me, also in memory research, whom I have known since graduate school: Mort Mishkin, Jim McGaugh (Volume 4), and Eric Kandel (Volume 9). They were all in my Presidential Symposium at the Society for Neuroscience Annual Meeting in 1994. Mort was unfailingly generous with Stuart and me when we were doing our monkey work. I had the pleasure of introducing him in 2016 when he received the NAS Award in the Neurosciences. Jim is at nearby University of California Irvine. I have visited him for conversation and advice on many occasions and was always the better for it. I wrote a book with Eric (*Memory from Mind to Molecules*, 2009, 2nd edition), an exhilarating experience, and in 2000, we did a fine piece on the history of neuroscience (*Science*, 2000, *290*, 1113–1120). Eric knows more neuroscience than anyone I know.

I have been driven most of all, I think, by the pursuit of facts and by the job of developing the evidence to make a finding convincing. The presentation should be not just compelling but also beautiful. I am almost more interested in the facts than in their interpretation, though I do know why I did what I did. I like a finding that implies the interpretation, or where the interpretation is obvious, and there is scarcely need for a Discussion section. I think I have sometimes fallen too much into developing experiments to counter work I find misguided, especially when a publication is directed at my own work. Deciding whether to engage in "defensive" experimental work or carry on with one's own program is a matter worth serious deliberation. My friend, physicist George Feher, once remarked, "You can't become a saint by showing that someone else is a sinner."

I have been surprised at the extent to which a scientist sometimes holds onto an idea, despite evidence that, so far as I can tell, completely dislodges it. For some, the idea seems to trump the data, as if the idea is too good to be wrong. I am often reminded of Charles Darwin's comment about his

contemporary, Herbert Spencer, who was inclined toward large ideas. In his gem of autobiography, Darwin wrote: "His deductive manner of treating every subject is wholly opposed to my frame of mind. His conclusions never convince me: and over and over again I have said to myself, after reading one of his discussions, 'Here would be a fine subject for half-a-dozen years' work' " (*The Autobiography of Charles Darwin*. Nora Barlow, ed., 1958, p. 109).

In 1993–1994, there were 20,000 members of the Society for Neuroscience when I served a term as president. It was a challenging time, as we were in the midst of deciding if we should bring the *Journal of Neuroscience* in-house and also find a new editor. I worked closely with my friend Carla Shatz, president-elect, and also initiated this History series (143 chapters through Volume 10), as well as what became 30 edited, broadcast-quality, 1-hour video interviews of leading neuroscientists, collected between 1994 and 2008. All of this is freely available at the Society's website.

The balance that one is meant to achieve between work and family eluded me, I am afraid, and my absorption in the work was certainly a large factor in the eventual dissolution of two partnerships. But these gifted me with four magnificent children with whom I have remained close: Ryan (1986), Luke (1988), Charlie (2005), and Caroline (2008). One thing that brought us all together was our Vermont house. In 1966, during my time at MIT, and using the poker winnings from Stanford as my share, two friends and I built a house in southeastern Vermont. We were going to build a standard A-Frame, but one of our roommates, a student at the Harvard Graduate School of Design, proposed that he design something for us. The result was a modest, cedar-shingled house overlooking a brook, which I eventually bought out from the others. Over the years, it became a regular vacation place for me and all four children, who love it and have visited every year of their lives.

Outside of science and family, there were two activities that claimed my attention, actually two games: Scrabble and poker. Scrabble is one of the great two-person games. I played tournament Scrabble until it was displaced by the writing of my first book (*Memory and Brain*, 1987). It fascinated me that this widely popular game, as played in tournaments, is miles apart from the game enjoyed by the average living room player. Even a middling tournament player (like me) would likely outdistance a living room player by 100 points or more per game. Tournaments are played with a chess clock with 25 minutes allocated to each player for the total game. Players know all 105 two-letter words and each of the several hundred three-letter words. It is a contest of letter management and the construction of words that use all seven of one's tiles. These words (Bingos), garner 50 bonus points, and three or four of them might be played in any one game. Players know how to rotate certain six-letter word strings through the

alphabet to find dozens of seven-letter words, most of which no one recognizes as regular words. For example, for the well-known string, SATIRE, one finds ATRESIA, ARISTAE, ASTERIA, BARITES, BAITERS, REBAITS, TERBIAS, ATRESIC, CRISTAE, RACIEST, STEARIC and on it goes. An example of an inside joke is: He had SATIRE plus a blank and couldn't find a Bingo.

I have continued to play poker ever since Stanford, finding private games in Cambridge, New York, and now in San Diego. Poker is endlessly absorbing. There is knowledge of the game, probabilities, the characteristics of the other players, and tactics. The private game that I currently play in was begun in 1964 by George Feher, who brought it to UCSD from the Bell Labs. The game happens every two weeks and goes for 5.5 hours. Poker in California is legal, so long as the game is not being run for profit. There are more than 20 different forms of poker (e.g., Hold 'Em, Omaha Hi/Lo, Badugi), each requiring seriously specialized knowledge. The very best players sit in mixed games where the game changes every eight hands. Outside our private game, I play two specific games myself (Stud Eight or Better, Big-O) and have occasionally indulged them at the giant casinos of south Los Angeles. I know little about Hold 'Em, currently the most popular kind of poker. I am a good player but am not at the level of the professionals. One finds parallels between poker and science. Each hand is a new experiment, which one should approach without bias. Probabilities bear out, and, as physicist Richard Feynman once wrote, "Nature cannot be fooled." One sometimes must give up a cherished belief. A promising idea is abandoned, an excellent starting hand is discarded. Considering the time I have invested in this hobby, I am glad to report that I have a lifetime positive outcome.

Coda

As recounted, my early enthusiasm for reading the literature effectively shaped my entire career. A 1971 paper on retrograde amnesia fueled the transition to human memory and human memory impairment. A 1978 paper on the hippocampus led to 21 years of work with nonhuman primates. I think this is all it took to have a satisfying career—the excitement I felt when I read those two papers and the possibilities I could imagine. The rest of it was that I loved it. My reading of the literature in the early days, however, and my enthusiasms, sometimes took me into unfamiliar territory. I remember once trying to describe a finding to Dale Purves.

"Who did it?" he asked.

"I think it was Westrum, something like that. Maybe Wes," I said.

Dale replied, "Wes Westrum was a catcher for the New York Giants."

Graduate Students	Postdoctoral Fellows
1970s	**1970s**
Neal Cohen	Douglas Wetzel
1980s	**1980s**
Ken Paller	Art Shimamura
Richard McKee	Jeri Janowsky
Frank Haist	Carolyn Cave
Wendy Suzuki	Gail Musen
1990s	**1990s**
Elizabeth Buffalo	Barbara Knowlton
Joseph Manns	Stephan Hamann
Nancy Rempel-Clower	Pablo Alvarez-Royo
Seth Ramus	Paul Reber
Edmond Teng	Jonathan Reed
	Craig Stark
	Heike Schmolck
	Erin Kitchener
	Robert Clark
2000s	**2000s**
Jeffrey Gold	Nicola Broadbent
Yael Shrager	Peter Bayley
Peter Wais	Daniel Levy
	Christine Smith
	Brock Kirwan
	Kristin Mauldin
2010s	**2010s**
Ashely Knutson	Zhuang Song
Annette Jeneson	Soyun Kim
Adam Dede	Zhisen Urgolites
Amber Ocampo	Nadine Heyworth

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