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Chasing memory: one man's epic quest

Gary Lynch has spent decades trying to understand how the brain processes new information so that we can recall it later.
By Terry McDermott, Times Staff Writer
First of four parts

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The first time I spoke with the neuroscientist Gary Lynch, the conversation went something like this:

Me: I'm interested in spending time in a laboratory like yours, where the principal focus is the study of memory. I'd like to explain how memory functions and fails, and why, and use the work in the lab as a means to illustrate how we know what we know.

Lynch: You'd be welcome to come here. This would actually be a propitious time to be in the lab.

Me: Why's that?

Lynch: Because we're about to nail this mother to the door.

Lynch is a neuroscientist at UC Irvine, where he has spent 37 years trying to uncover the biochemical mechanisms of memory.

He has, for almost the length of his career, been trying to answer essentially a single pair of questions: What happens in the brain when a human being encounters a new experience so that he or she can recall it at will tonight, tomorrow, in 2025? And what goes wrong when we can't remember?

This second question has in the last several years taken on great weight.

We are on the verge of a dementia pandemic. It is estimated that by 2040, 100 million people worldwide will suffer from Alzheimer's disease, Huntington's, Parkinson's or some other form of dementia. Science has been able to do precious little to combat these diseases, in large part because the understanding of the underlying cognitive processes has been meager. Thousands of scientists have spent countless years seeking and largely failing to unearth the secrets within the human brain.

Medical advances have allowed more and more people to live longer but have been unable to relieve longevity of its principal bane -- the breakdown of mental processes, especially memory. When memory loss occurs, it seldom fails to impress upon its victims and those who know them the extent to which our memories constitute our selves.

That breakdowns occur is not surprising. Consider: You're 50 years old. What's your time in the 100-yard dash? How does that compare to the 18-year-old you? Why would your brain be exempt from declining in analogous ways? It isn't. So much goes wrong so often that many malfunctions are considered ordinary and are often referred to collectively as normal cognitive decline.

Before that first conversation with Lynch, I already knew that he had been an often polarizing figure in his field, that he had a reputation for being pugnacious, and that he had been uncannily right about a lot of things over a very long time.

In the subsequent two years, I spent a great deal of time in his lab. I spoke with the other scientists who worked there and observed their experiments; I read papers they and others published; I learned how to perform some of the most rudimentary tasks of their basic experiments. But what I did mostly was talk to Lynch. Or, more to the point, listen as Lynch explained mammalian biology and brain science.

Listening to Lynch often entailed following swooping, exhilarating flights over time and intellectual terrain. Bear with me, he sometimes said, this might not seem connected to what we've been talking about, but it will circle back. Ten, 20 or 30 minutes later, often after side trips to ancient Rome or Yankee Stadium or Bismarck's Germany, it did.

Lynch almost always spoke in such a way that his huge ambition, self-regard and lack of pretense were vividly displayed. He was unreserved, witty, juvenile, insightful and learned in ways that were surprising. He was as apt to quote Cormac McCarthy as Gregor Mendel. He made on-the-fly references to, among many other things, left- handed relief pitchers, Moses, British naval history, the stock market, Kaiser Wilhelm II, Maxwell's equations, the ur-city of Ur, Darwin, Dylan, Kant, Chomsky, Bush, Titian, field theory, drag-racing, his father's perpetual habit of calling him -- intentionally -- by the wrong name, his career as a gas jockey at an all-night service station, Pickett's charge at Gettysburg, Caesar crossing the Rubicon, and the search for the historical Jesus.

Christine Gall, Lynch's frequent collaborator and longtime significant other, said: "Gary just has more RAM than other people. He can access lateral information that most people can't. It isn't like he has to think and remind himself. It's right there. He has access to it. To have that available to inform you, to make the next cognitive leap -- that's his strength."

That leaping ability has earned Lynch as much trouble as reward. He never shies from proclamation based on his intuitions, nor from criticizing those not privy to his insight.

"That is what amazes me," he said. "People will walk in who are very sensible and intelligent biologists and tell you, 'Memory is this.' And you go, 'How in the hell could it possibly be that? I didn't think it was that when I was back at Our Lady of Fatima Grade School. I mean, I didn't think it was that when I was working at the all-night gas station. For crying out loud!' "

One result of this perhaps excessive straightforwardness has been a constant war with the neuroscience establishment, with university administrators and colleagues at Irvine. But whatever his difficulties, Lynch has slogged along, making hard progress documented in more than 550 published papers, some of which are considered classic and are among the most frequently cited works in all of neuroscience.

As a corollary to his basic research, Lynch has sought ways to counter the various afflictions that erode the brain's abilities. Working with chemist Gary Rogers, he invented a new class of drugs called ampakines, which, if they worked, would not only improve memory, but would make the brain perform better in numerous other ways. Drugs of this sort, called cognitive enhancers or, more simply, smart pills, have been the Holy Grail of brain research for a century.

Like much contemporary drug research, ampakine development has been slow going, but by the time I met Lynch, versions of his drugs were being considered by the Food and Drug Administration for a series of clinical trials, which should largely determine whether their substantial promise could be fulfilled. Success would be a signal moment in neuroscience history.

By chance, the ampakine drug trials would get underway at the same time the memory research in his lab seemed headed toward its own finale. Lynch had a sense that answers he had spent a career chasing were at hand.

He was alternately eager at the opportunity and despondent at the likelihood of failure. He knew, as every research scientist does, that almost everything almost always goes wrong. If, over time, science can be viewed as the steady extinction of ignorance, in the near term, on most days, ignorance wins hands down.

"If you're good, if you're any good at all, you put yourself in a situation where reality could come around and -- WHACK! -- knock you down. That's what you really are afraid of. If you don't have that, you're not playing science," Lynch said.

He was definitely playing science now. With the drug research and the fast-approaching end to his torturous journey in what he once characterized as a gulag of unyielding biology, he had a rare opportunity -- a shot on goal, he called it.

"Come to the lab," he said. "This could get interesting."

Lynch Lab

Save for lynch, Lynch Lab was empty just before New Year's 2005. Much to Lynch's chagrin, everyone was vacationing.

The lab had just developed a new technique that he thought would allow researchers to visualize the physical trace of memories, and in doing so resolve long-standing, fundamental debates in neuroscience.

This new technique promised to answer conclusively what had been supposition, and to answer it in such a way that you would literally see the result. And people went on vacation?

Most of the space in Lynch Lab was taken up by two parallel ranks of standard lab benches, complete with faucets, hoses, beakers, stocks of chemicals, pipettes, scales, reference books and undergraduates. Lynch and the lab's senior scientists had offices on the perimeter, but most of the experimental work was done out on the benches.

Lynch could almost always be found in his office, writing or reading, and chewing on a cigar if he had one or a plastic cafeteria fork if he didn't. No matter whose name was on them, almost all of the journal papers that issued from the lab were written by him.

He has an open, almost guileless face, so helplessly expressive that your first impulse is to invite him to a poker game. The years have begun to accumulate, however, cutting deep lines. He is about 6 feet tall, rail-thin but for the beginnings of a belly, with tangled, graying hair that has relaxed considerably from its Charlie Manson heyday. He usually dresses in high-quality, untucked, casual clothes -- Klein, Boss and Zegna shirts and jeans and well-worn chukka boots.

His corner office is spare and clean -- a large glass-top, metal-frame desk; a dual-monitor Mac workstation; a few potted plants along broad, undraped windows. He has a telephone on his desk, but it is often unplugged. He sometimes goes for weeks without reading e-mail. The only decorations on the walls are a single small plaque honoring him because his papers were so often cited by other scientists, and a pair of large abstract paintings of brain interiors, which are mostly purple and surprisingly pleasant.

Except for a congregation of Starbucks decaf cups, he is fastidious. There is almost never more than a single pen and a pad of paper on the desktop; he keeps a spray bottle of glass cleaner handy to scrub it, which he does religiously. He usually has a bottle of whiskey and a brace of glasses stowed among the plants. Before serving, he scrubs the glasses with the same care he applies to the desk.

The duties of a university scientist leading his own lab are manifold. Foremost, the existence of the lab depends on his ability to fund it. He is an employee of the university, but also a profit center. He must attract grants, from which the university takes a significant cut, to pay the basic expenses of his laboratory: salaries, equipment, supplies.

The overwhelming majority of grant money comes from the federal government, most through the National Institutes of Health. The competition for money is intense and often leaves normally placid scientists swearing like deckhands. Lynch, whose lab has been funded mostly by the federal government at around $1 million per year for decades, was no exception.

In part because of the constant threat of extinction, neuroscience labs -- even those that don't have Lynch in them -- are not the happiest places. There is tension and fear and jealousy and a near-constant sense that careers are about to be made or, more commonly, missed. Such fraught situations call for careful, considered management.

Due to a lack of interest, or possibly ability, which can be the same thing, Lynch seemed to run his lab like a man on a midnight beer run, running pell-mell down the aisle, throwing things, many of them unhealthful, into the cart and hoping there would be enough for everybody when he got back to the house.

Which is to say, although it was obvious to him, it wasn't always clear to others what Lynch was up to.

In addition to providing money, the lead scientist, in the academic world called the principal investigator, is the intellectual leader of the team. Lynch did very few experiments himself, but designed, assigned or approved virtually all of what everyone else did. He would hate to admit it, but he was a dictator.

The 'free-ride guy'

The youngest son in a disintegrating Irish Catholic working-class family in Wilmington, Del., Lynch earned scholarships to Catholic high school, then -- "always a free-ride guy" -- the University of Delaware.

The ride ended abruptly when he was kicked out for partying. He worked odd jobs until he was readmitted. Because Lynch's main interest in college was to have a good time, something had to change. When he came back, he changed majors from engineering to psychology for, he said, two reasons -- engineering students spent weekends building electric circuits and, as important, there were very few girls among them. Lynch chose psychology, he said, because there were plenty of girls and no weekend work.

Lynch, in spite of his professed laziness, excelled and earned a graduate scholarship to Princeton, where he quickly determined he was much more interested in mucking around inside the head than standing outside it and asking questions.

He earned his doctorate in psychology in 1968, just three years after enrolling. Soon after, he received a job offer from UC Irvine. The university was so new it hadn't yet graduated its first class.

The offer was to teach in the psychobiology department. Lynch had not completed a single college course in biology. (Too many details, he said.) He had never been to California. But one of the first of those now ubiquitous lists of the best universities had been recently published. UC Berkeley ranked No. 1 in the world.

"The thrill I felt was -- it's the people's university," said Lynch. "That's a public university. Oxford, Cambridge are down here; Harvard's down here; Princeton's down here. The best university in the world is a public university. I thought, 'Man, we are so on the right track.' That inspired me. . . . I thought, 'This is it; this is finally it.' In the face of people working on great things together in the sunshine, in the eternal summer of California, privilege falls away. What could be more beautiful?"

Irvine then was not far removed from its ranch-land past. There were cattle grazing on the hills above the campus and cowboys chasing them. Almost overnight, the university became a center of brain research.

Neuroscience, too, was young, and there was a sense broadly shared that the human brain, one of the great frontiers of science, was about to be colonized -- although from what direction or by whose army was unclear. Biologists, chemists, anatomists, psychologists, mathematicians, even philosophers and physicists, all suddenly calling themselves neuroscientists, plunged into the field. No one knew where they were going, and no one wanted to be left behind.

Memory as a subject of inquiry and wonder is as old, perhaps, as man. The ancient Greeks variously proposed that memory and other mental processes were a function of the heart, the lungs or the brain, which eventually became the agreed-upon site. Beyond locale, however, little was learned about the processes of mental activity for the next 2,000 years.

Although the great Spanish anatomist Santiago Ramon y Cajal proposed in the late 19th century that the brain was composed of tiny cells called neurons and that memory might be stored at connections between neurons, there were plenty of scientists who thought the whole mental apparatus too ineffable, too mysterious a subject to yield to laboratory examination.

The seminal event in the modern history of memory research occurred by accident in 1953. In an effort to stop horrific epileptic seizures afflicting a young Connecticut man, a neurosurgeon named William Scoville removed a portion of the man's brain. The surgery stopped the seizures but rendered the man, known in the literature as H.M., incapable of forming new memories. His memory of events before the surgery was uninhibited.

A main portion of the brain that Scoville removed was a temporal lobe structure called the hippocampus. The fact that H.M. could no longer form memories but could recall older ones suggested strongly that the hippocampus was crucial to making but not storing memory. It immediately made the hippocampus the central focus of memory research, a position it had maintained when Lynch, just 26, arrived in Irvine in 1969.

Lynch was wild-eyed, bushy-haired and bearded, a man of his time -- a bit too fully, perhaps. It was the '60s, it was Southern California, land of eternal light and endless good times. Lynch lived in a party pad on Balboa Island.

By every account, including his own, Lynch ate badly, drank heavily and slept hardly at all. There were days he seemed to consume more cigars than calories.

"Gary doesn't sleep," said Michel Baudry, a 10-year veteran of Lynch's lab. "He's incredible. I don't know how he survives."

Another researcher, Kevin Lee, recalled that for a period in the 1970s, the only things he ever saw Lynch eat came out of a vending machine, a *single* vending machine. His main meal consisted of salted peanuts mixed into soft drinks.

"You know, Gar," Lee recalled telling him, "you might think about diversifying your diet. Nothing radical, but hey, man, try a new machine. Have some chips."

Lynch's diet was of a piece with his extreme work habits, which typically included seven days a week of 12-hour or longer shifts in the lab, often followed by monumental bouts in the nearest bar.

Given 400 square feet of lab space and $900 to equip it, Lynch quickly made discoveries having to do with the brain's ability to repair some damage to itself after injury. It had generally been thought that the brain was static, that it did not produce new cells or structures after it reached maturity. Lynch and others began to wonder whether the brain did not possess more malleability, what was called plasticity.

In 1973, just as Lynch was expanding his investigation of brain plasticity, a pair of scientists in Europe discovered that when they stimulated the hippocampus with electric current intended to simulate brain activity, connections between hippocampal cells were strengthened and, more important, those strengthened connections could be retained indefinitely. They called the phenomenon long-term potentiation (LTP).

The combination of brief stimulation and long-lasting effect matched the key characteristics scientists had long associated with memory. Lynch and others wondered whether LTP was the biochemical process underlying memory. A global race was on to prove it. Thirty-two years later, Lynch hoped he was near the end of it.

'A strange place'

Lynch lab has been staffed over the years by a succession of visiting scientists, grad students, postdoctoral researchers, dope peddlers, English majors and whoever else was swept up in Lynch's often irresistible aura.

All of the inhabitants have been very bright, some brilliant. A number have gone on to chair university departments, to found successful companies or to publish distinguished papers, but when they were in the Lynch Lab, there wasn't much to recommend them to civil society. Any hint of future distinction was obscured by the chain-gang grind of life in the lab.

Lynch's extraordinary drive and ability to make every person feel that he or she was working on the single most important experiment in neuroscience history was the oxygen the lab lived on. Especially in the early years -- a period Lynch called "the boy lab" because of its testosterone-driven internal competitions -- the lab was a woolly place, not far removed in its culture from a Neanderthal cave. The guy with the biggest club generally got his way. Lynch, while not at all physically imposing, had a ferocious temper and never left a shadow of a doubt about his willingness to swing whatever was at hand. The history of the place was littered with battered telephones and drywall with holes suspiciously the size of baseball bats and fists.

"That's part and parcel of the fire that burns in him," said Lee, who now chairs the neuroscience department at the University of Virginia. "The phone on the wall? It just looked like a baseball sometimes."

"He never really hurt anybody physically but himself. Although there were people with emotional scars, I can tell you," said John Larson, now of the University of Illinois at Chicago.

Lynch said: "That lab was a strange, strange place. A lot of weird, weird, different kinds of people. The dean would look at it and say, 'That's a strange damn place.' I'd answer: 'Have you looked at me?' "

Amy Arai, a native of Japan, recalled the culture shock she felt when she joined the lab in the 1980s. "In Japan, everything is very formal. Scientists wear jackets and ties to work every day. Here in Irvine, nobody did that," she said. "I had a hard time even locating Gary. . . . I wandered around looking for him. There were lots of people wandering around, including one particularly scruffy guy I saw in the hallways, shirt always untucked and dirty. I'd sort of hold my breath when I passed him in the hall. I thought he was a janitor."

One day, weeks after arriving, Arai was summoned to Lynch's office, which was removed from the rest of the faculty offices in a double-wide trailer next to a parking lot. Arai walked in and found the trailer empty except for the "janitor," who was sitting behind a desk smoking a cigar. It was Lynch.

Baudry, a Frenchman, toured labs in the United States for five weeks in 1978, then went back to Paris and told his professors he was going to join Lynch. Baudry recalled the reaction of Jean-Pierre Changeux, the rising star of French neuroscience: "He looked at me. He said, 'You're crazy. Gary Lynch? The hippie of neurobiology?' I said, 'I'll take my chance.' I went to Gary's lab, and it really was something different in its ambience. All these wild people. The contrast with Paris -- fields, cows around the campus. I thought, I have to give this a shot. It really was the Wild West. And Gary really was this wild person."

Lynch still draws an off-kilter collection of researchers. His latest lab -- the "girl lab," as he described it -- included a grad student who wasn't officially assigned to the lab, a postdoc who ended up there by virtue of being kicked out of her original department, and a preternaturally talented undergrad who was hanging out only long enough to decide which med-school scholarship to accept. The senior scientists, except for one man who never left his private office, were three women, who seemed to speak with one another as seldom as possible.

Work was assigned largely by Lynch's judgment of who could do what. If an undergrad was able, he would find himself in the middle of crucial experiments.

The lab has changed locations and varied in size over time -- anywhere from three dozen people to as few as six or seven. In January 2005, there were around a dozen regular members, with students floating in and out.

Much of the work was some variation of two basic LTP experiments. One involved isolating single neurons, which, using high-powered microscopes, were identified, then pinched with a clamp to hold them in place. This was exceptionally tedious. Researchers could go entire days without successfully clamping a single cell.

The other experiment entailed placing a thin slice of a rat's hippocampus in a nutrient bath in which it stayed alive for hours, then imposing one of a variety of conditions on the slice -- usually, infusing it with chemicals known to inhibit or incite certain molecular reactions -- then stimulating the slice with a precisely timed, placed and quantified electric impulse and measuring what happened to that impulse.

What the scientists were trying to find out by blocking or inviting the action of certain molecules was what role they played in LTP. Theoretically, you could determine all of the principal agents by this process of elimination.

In practice, people spent extraordinary amounts of time -- hours at a sitting, days or weeks in succession -- staring at graphical renderings of the results on computer screens. It was not work filled with obvious drama or even, except for making the occasional note in a lab journal, movement. The lab was quiet -- no music; no telephones; low conversations, when there were any at all.

Lynch lived in dread of being scooped on discoveries. The residents of the lab did not gush in praise of his patience. He strode among the benches several times a day to see how much progress was -- or, more usually, was not -- being made.

Lynch talked often about hating the day-to-day process of science, the actual experiments. He could hardly bear to wait for them to be done to prove what he suspected to be true.

One day, explaining his distaste, Lynch said, "There is so damned much housekeeping. The problem is, biology is a very horizontal science. You have this result over here, that one over there. None of it lines up."

His lack of enthusiasm for working on the bench meant that he needed others who were both capable and willing to do it. No wonder he was unhappy about the rash of holiday vacations.

'Shadow land'

The person lynch was most unhappy with was Eniko Kramar, a postdoc neurophysiologist who was running the crucial experiment Lynch expected to prove his basic theory of memory encoding. Kramar could hardly be regarded as a slacker. She typically worked longer and harder than anyone in the lab, excepting Lynch.

Having come relatively late to neuroscience, she was approaching a point in her career where she needed to make discoveries, then move on to lead her own lab, or remain locked in subordinate roles. She had become, like Lynch, a virtual scientific monk, paring away other activities in her life until all that remained was the lab. Unlike Lynch, she had actually had a wide range of outside interests -- family, friendships, athletics.

Although it seemed to her at times that the more she did, the more Lynch demanded, they were in important respects a good team. He was a synthesizer. She was a pointillist, a technically minded bench scientist who took care to not extrapolate beyond the results on her screen. She sometimes found even those suspect, wondering if some mistake hadn't deceived her into false optimism.

When Kramar returned from her brief Christmas holiday, she plunged back into the experiment, which she had been planning since the previous summer. It involved using a novel staining technique that would let the researchers actually see changes in neurons.

A key part of Lynch's conception of LTP, and thus memory, was that the process initiated a micro-scale remodeling of the interior skeleton of cells at synapses.

It is generally agreed that memory is somehow built out of networks of brain cells called neurons. How those networks get built is the central question of memory research.

Researchers have established that when you experience a sensation in the outside world -- perhaps seeing, smelling or touching something -- the sensation is translated by the sensory organs into an electrical signal that is routed to neurons in the brain, where, if the signal is strong enough within individual neurons, it causes chemicals called neurotransmitters to be released onto neighboring cells.

Neurons are not physically connected to one another. There are tiny spaces called synapses between them. The neurotransmitters travel across the synapses. Think of the neurotransmitters as keys. On the surface of the neighboring neurons are molecules that receive the neurotransmitters. These are called receptors. Think of the receptors as locks. When neurotransmitters attach to receptors on the surface of a receiving cell, when the key opens the lock, channels open into the cell.

It is because the neurons are not physically connected that communication between them is never certain. You never know whether a key is going to find a lock. This is thought to be why any cognitive activity, including memory, is approximate. Sometimes the connections are made; other times they are not.

The LTP hypothesis can be summarized by saying: After two neurons have successfully made contact once -- that is, after the neurotransmitters have attached to receptors -- the next time the original cell releases its neurotransmitters, there is a much greater chance the neighboring cell will receive them. There is a greater chance a key will find a lock.

Lynch's longtime goal was to figure out why. The general outline of his hypothesis was this: Once a neurotransmitter attaches to a receptor, opening a channel into the cell, calcium pours through the channel, setting off a chemical cascade inside. The end result of that cascade is an interior reorganization of the cell.

A key molecule involved in the interior remodeling is called actin, which is a structural protein used throughout mammalian biology to build internal cell scaffolds. In the same way the outside of a house reflects the shape of the frame beneath it, when an internal cell scaffold is altered, the exterior of its cell is changed too. In this case, Lynch thought a portion of the cell would become squatter, with more surface area. The greater surface area provides space for more receptors. The greater the number of receptors, the greater the chance of a neurotransmitter finding one and making a connection between the two cells.

The lab had recently developed a method in which the actin scaffold proteins could be labeled with a dye. The labeling would occur only after the actin changed shape; in lab terminology this was referred to as polymerized actin.

The idea of Kramar's experiment was that after inducing LTP with the usual electric stimulus, portions of the cells would restructure, creating polymerized actin. Because the actin was stained, you could actually see it under a microscope. If you could see it, it would mean Lynch had been correct in proposing that the whole physical remodeling, the actin polymerization, was the end result of LTP.

That reorganization, in turn, strengthened the connection between cells; networks of those neurons with strengthened connections constituted the underpinning of memory.

When Lynch had originally proposed this sort of rapid structural change at synapses, many in the field were skeptical. Eventually, most researchers came around to the view that some sort of structural change occurred, but it was taken more as a matter of faith. Even many who believed the structural rebuilding occurred thought newly synthesized proteins from the cell nucleus had to be sent to the synapse to do it, and they spent an awful lot of time looking for those proteins.

Lynch thought it would take too long for the proteins to be manufactured in the cell nucleus; events were already underway, and the material needed to complete the job was on hand.

Imagine a construction crew framing a building. If the protein synthesis believers were right, the carpenters would have to call a warehouse every time they needed a nail. Lynch proposed that the crew had the nails right there in their belts. This experiment was intended to provide proof.

"We're in the penumbra, the shadow land," Lynch said. "And now comes the moment of moments."

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