

The stuff of memories

Science inches closer to explaining how we remember and why we forget

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You never know when you are making a memory.

–**Ricki Lee Jones, singer**

In fact, there's almost never a time – or at least a waking moment – when you're not.

“Even if you try to clear your mind, say by listening to a song, you're making memories about that song,” said John Wixted, chairman of UCSD's psychology department and a memory researcher.

To be sure, the memory may be fleeting, the song soon forgotten. But that, too, is part of the marvel of memory. Why do we remember what we do? Why do some memories stick, but others do not? Why can't we recall the first few years of life, when our brains were like sponges, yet we retain other recollections for as long as we live?



CRISTINA MARTINEZ BYVIK
/ Union-Tribune

Such questions have long been the province of philosophy, but science is increasingly offering definitive, empirical answers. Equipped with new imaging technologies and an ever-fuller understanding of brain biology, researchers are peeling back and parsing memory's mysteries.

The long view

In his book, “The Odd Brain,” anthropologist Stephen Juan writes that the average brain on the average day generates about 70,000 thoughts. Many of these thoughts – including those that never rise to the level of consciousness – become memories.

Memories are categorized in many ways, most broadly as either short-term or long-term. Short-term memories last only as long as they are useful, from fractions of a second to mere minutes. Long-term memories can last a lifetime. They define us.

“We are not who we are simply because we think,” write neuroscientists Larry Squire of UCSD and Eric Kandel of Columbia University in their 1999 book, “Memory: From

Mind to Molecules.” “We are who we are because we can remember what we have thought about.”

Long-term memories, however, begin as short-term. But how? Scientists think they know part of the explanation.

Imagine a countryside stroll on a sunny, windy day. You see a rabbit romping through a field of flowers. Your brain is bombarded with sensory input, which is sent to different parts of the brain keyed to different sensory experiences. These brain regions, from the occipital lobe that handles vision to Heschl's gyrus, part of the auditory system, process and encode the new data. As the information moves from neuron to neuron, it alters the structure of synapses it passes through.

“Every time information runs through it, the brain changes. It becomes a new machine,” said Terry Sejnowski, a computational neurobiologist at the Salk Institute.

Neurons transmit information (in the form of electrical impulses) along an extension called an axon and receive information through dendrites. In the tiny gap where dendrite meets axon lies the synapse. To overcome the gap, neurons release chemicals called neurotransmitters that bind to specialized receptors on the dendrite, thus relaying the message.

Whenever this happens, the synapse is changed and certain receptors are strengthened. If the information is short-term – let's say the sight of that running rabbit isn't particularly interesting – then the synaptical change is temporary. The pattern of neural firings created by the information fades, and the memory is quickly forgotten.

To become a long-term memory requires a permanent alteration in the structure and nature of the synapse. This can happen if a short-term memory is repeated often enough. “For example, if your cat learns to connect the sound of a can opener with food,” said Douglas R. Fields, chief of nervous system development and plasticity at the National Institutes of Health.

“But to strengthen a connection between neurons permanently, some growth process must take place that expands the size of the synapse or sprouts new synapses. This requires that genes in the nucleus of the neuron become activated to make the proteins necessary for the synapse sprouting/growing process.”

The act of forming long-term memories is really a cascade of biochemical processes. The brain needs time to make a long-term memory, a job involving lots of players: modulating neurotransmitters like dopamine and serotonin, synapse-building proteins and, of course, genes.

The precise role of genetics in memory is unclear, but obviously memory varies by individual genome. Some people simply have better memories. A recent study by Dietrich Stephan of the Translational Genomics Research Institute in Phoenix offers one

potential clue: It found that participants in a memory skills test who placed in the top 25 percent possessed a different variant of a gene called kibra than those who placed in the bottom 25 percent.

Forget me not

But the importance of memory is not really about remembering lists of words or even past events. It's about predicting the future.

“We no longer stick hairpins in electrical outlets because we learned from this experience as kids,” said Fields. “In order for a memory to move into long-term memory, it must have some survival value. Your brain learned the hairpin in the electrical outlet lesson with one experience, but it took a few years to see the survival value of learning that 7 times 8 equals 56.”

Many survival lessons involve emotion, such as fear, anger or joy. Emotion elevates the status of any would-be memory. When you experience an emotional or stressful event – for example, witnessing a traffic accident – your body automatically releases hormones like cortisol and adrenaline that sharpen faculties and physical abilities, thus boosting your chances of survival if the event turns dangerous.

These hormones flood the brain's hippocampus, a seahorse-shaped structure deep in the forebrain that helps regulate learning, memory and emotion. The hippocampus is studded with receptors keyed especially to chemicals like cortisol. The detection of stress hormones, linked to incoming sensory data about the traffic accident, tells the brain that this is a memory of greater import. Stress hormones accelerate the transition from feeble short-term memory to durable long-term memory.

Memory probably works the same way in both men and women, say researchers, but emotion highlights a difference. Women form and remember emotional memories better than men because, it's suggested, their hippocampuses are larger, as is the part of the brain responsible for processing observed emotions in others.

Whatever the memory, however, it's stored the same way. The human brain likes associations and packs away its memories accordingly. Neural patterns representing memories share common connections, like a jumble of string criss-crossing itself. As soon as one part of a neural pattern is stimulated, the whole pattern follows – and then perhaps many other linked patterns or memories.

The aroma of a particular perfume, for instance, might trigger the memory of an old girlfriend, which might in turn stimulate connections to memories of what the girlfriend looked like, her parents' names or the fact that they never liked you.

But knowing that memories are complex neural patterns doesn't fully explain how they are stored.

“If memories are stored as changes to molecules inside brain cells – molecules that are constantly being replaced – how can a memory remain stable over 50 years?” asked Sejnowski in an essay published earlier this year.

His hypothesis: Old memories aren't stored inside brain cells, but outside them in a tough, tangled matrix called the extracellular space. If neurons are bricks, the extracellular space is the mortar, composed of hardy, fibrous macromolecules called proteoglycans that are replaced very, very slowly. Like scar tissue, the extracellular space doesn't change much over time.

Sejnowski's hypothesis is based on early research involving interaction between motor neurons and muscle cells. When the former activates, the latter contracts, producing movement. In experiments, when researchers crush a particular nerve cell, it regrows to its original junction, forming a new, specialized terminal ending with the muscle cell. The same thing happens even if the muscle cell is also killed.

The “memory” of this contact, suggests Sejnowski, came from the extracellular matrix surrounding the junction between neuron and muscle. Something similar might be happening in the brain, too, according to Sejnowski, with the extracellular matrix surrounding the synapses keeping neurons connected and constant even as molecules inside the neurons change.

It's possible to test this idea, using genetically modified animals in which specific components of the extracellular matrix have been selectively degraded or knocked out.

“If I'm right,” Sejnowski said, “then all your memories – what makes you a unique individual – are contained in the brain's exoskeleton.” One day, he said, it might be possible to stain this memory exoskeleton and actually see what memories look like.

Remember everything?

What if you remembered everything? There are people who can.

Earlier this year, James McGaugh, a neurobiologist at UC Irvine, and colleagues published a six-year study of a 40-year-old woman whose memory is so comprehensive and detailed that she can recall – vividly and instantly – almost every detail of almost every day of her life.

While the woman (who remains unidentified for privacy reasons) reportedly led a mostly normal life, her perfect memory made it hard to let things go, to move on. “People are not meant to be tape recorders,” said McGaugh.

Fortunately, the memories of most people are far less dependable. Their brains sort through and eliminate nonessential stuff, a process that begins when new information is first perceived.

You are much more likely to remember something if you give it your undivided attention, according to Michael Rugg, a professor of neurobiology at UC Irvine, and if the attention is focused upon the meaning of the event, rather than superficial attributes like physical appearance.

Part of what's happening, he said, is that when you pay attention, the brain boosts production of the neurotransmitter dopamine, which acts to open or widen doors between communicating neurons. The more dopamine present, the more likely a memory is to be recorded as important and long-term.

Mouse studies have proved this point. Mice genetically modified to produce less dopamine struggle in maze tests measuring memory, while mice with more dopamine remember things longer.

Sleep, especially the type known as non-rapid eye movement, is essential to the process of pruning away excess memories. This is also the perfect period for constructing complicated, time-consuming long-term memories, said Sejnowski. “The brain gets eight hours to do the job.” It should surprise no one, then, that people who are significantly sleep-deprived frequently suffer from memory problems.

Keep it in mind

Joseph LeDoux, a neuroscientist at New York University, notes that memory isn't any single thing. Different brain systems are capable of recording and storing information about life experiences. A memory can reside in one place, but be accessed by another.

“Information is handled and processed within certain regions irrespective of what's happening elsewhere,” said Sejnowski. “It gets bounced back and forth. It gets processed and created within cells. Synapses can be generating information on their own.”

What distinguishes humans isn't so much our basic brain machinery. Many animals – some as simple as marine snails – handle incoming information much like people do. What differentiates us, said Sejnowski, is what we can do with that raw data. Our brains have evolved incredible abilities to add and subtract known and unknown molecules to the information, like myriad spices to a dish. A snail may notice the water is colder, but it cannot recollect what the temperature of the water was yesterday, predict what it might be tomorrow or complain that it's altogether too cold.

There are aspects of memory, human and otherwise, that continue to defy scientific answers. No one, for example, can yet explain why people cannot remember the first few years of life. The phenomenon is called “infantile amnesia,” the profound loss of memory associated with the start of life.

“This may be because the brain is immature (at the time) and we no longer have access to those memories,” said McGaugh at UC Irvine. “But really, there's no satisfactory explanation. I guess we'll leave that to the next generation of neuroscientists.”

McGaugh, a memory pioneer who has been studying the subject for decades, laughs at the thought. It's a reminder of how much we still have to learn – and remember.

So that we can then learn even more.

CLASSIFYING RECOLLECTIONS

Memories can be classified in many ways, but most simply by information type, temporal direction and duration.

In terms of information type, there are two kinds. Declarative memories require conscious recall; procedural memories do not. A declarative (or explicit) memory is

remembering what you got for Christmas last year. A procedural (implicit) memory is recalling how to ride a bike or drive a car. It's a learned skill that demands no conscious effort. It's automatic.

Temporal memories relate to time. A retrospective memory looks backward. It recalls the past. A prospective memory is information to be remembered in the future. It's a memory of future intentions, such as tying a string around your finger to remind yourself to put out the trash.

Most important, though, may be memory defined by duration. There are three basic categories: sensory, short-term and long-term. Sensory memories correspond with that initial moment when something is perceived. You touch a hot stove and instantly recognize the feeling/pain of heat. The moment of recall lasts just a fraction of a second.

If the sensory input lingers, it becomes short-term memory, information that persists in the mind for seconds to minutes. This is data usable in the moment, such as recalling a phone number long enough to dial it. Experiments have shown that people typically retain between five and nine distinct bits of information at a time in their short-term or “working” memory. The average is seven, which perhaps not coincidentally is also the length of a phone number.

Short-term memories can become long-term, usually through repetition or meaningful association. They can be exceedingly durable, lasting a lifetime.

—*Scott LaFee*

A two-part series

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