SKIZZOMAT

Shadows of the past

Clare Wilson goes on a quest to discover how we create memories and how they create us

IN THE Harry Potter films, they are silver streams that can be teased from the head with the tip of a wand. In the recent Pixar movie *Inside Out*, they are small glowing balls, stored in vast racks of shelving in our minds. But what does a memory really look like? How does your brain take information from the outside world and cache it for later retrieval? Where are your brain's storage vaults, what do they look like and how do they work?

A lot of us would be intrigued to know the answers to such questions – yet they are surprisingly hard to come by. Memory researchers have often seemed to take a piecemeal approach. Some focus on the minute details of what goes on in connections between brain cells. Others try to understand the subjective experience of memory – such as how, for Marcel Proust, the taste of a madeleine cake invoked detailed scenes from his childhood. However, they seldom consider the bigger picture of how the brain changes when we create a new memory.

Yet surely the answers must be out there – so I began a quest to find out what a memory really looks like. My aim was to see what goes on inside my head when I relive an experience or recall a fact but I also discovered a lot more. Memories, it seems, are the ghosts in the machine that make each of us unique.

Some early seminal work on memory was done in the 1960s on sea slugs. These creatures grow up to a foot long and have giant nerve cells to match. Their outsize bodies make it possible to watch what happens when a new memory forms.

Ordinarily, electrical impulses in one neuron spark the release of chemicals that cross the gaps, or synapses, between nerve cells and may trigger a second neuron to fire. Those early studies revealed that when sea slugs learned a simple response to a stimulus some of their synapses were strengthened. An impulse in the first neuron was now more likely to trigger the second to fire (see diagram, page 38). This turns out to be the basis of memory in any animal with a nervous system. The work was so pivotal it earned neuroscientist Eric Kandel of Columbia University in New York a Nobel prize in 2000.

But it doesn't answer my question. The human brain contains an estimated 100 billion neurons, each thought to connect with, on average, 1000 others. That gives us something like 100 trillion synapses. When I create a memory, which of those synapses are strengthened?

A major step along the route to answering this question came from one of the saddest tales of modern neuroscience. In 1953, Henry Molaison – known for a long time only by his initials, H.M. – had an operation that went badly wrong. The surgeon had been trying to remove brain tissue that was causing his epilepsy. Molaison's seizures originated in the hippocampi, a pair of structures, either side of the brain, whose Latin name reflects their supposed resemblance to a seahorse. So the surgeon took them out.

The consequences for the 27-year-old Molaison were huge. Unable to hold a thought in his head for long, he needed care for the rest of his life (see "Groundhog day every day", page 39). But equally profound was the impact on neuroscience – we have learned volumes from the way the surgery destroyed some of Molaison's abilities but spared others.

Molaison seemed to retain most of what he knew before the operation, suggesting that while the hippocampi are crucial for forming new memories, they are less important for storage. His short-term memory was unaffected, too – he could retain information for 15 to 30 seconds but no longer. In addition, Molaison's brain damage revealed that there are some important subdivisions of long-term memory (see "Hold that thought", right). He could still learn physical skills, like riding a bike. But he had problems forming new memories of things that happened to him and learning new facts.

The long and short of it

The hippocampi seem to be crucial, then, for the sort of memories that are central to our personal and intellectual lives. So I go to meet Hugo Spiers, a neuroscientist at University College London who has made a career of studying them. In his office is a life-size rubbery model of the human brain. While he is making me a cup of tea, I pick it up and pop out one of the hippocampi. For something so vital, it's rather underwhelming – and disappointingly unlike a seahorse. In fact, it's about the size and shape of a chipolata – an unlikely seat of human learning and mental time travel.

Spiers puts me straight. They are by no means the only part of the brain required to make a memory, he says. While the hippocampi are important and dominate current research, memory also involves the cortex, the outer layer of the brain that handles our complex thoughts and sensory perceptions of the world.

Say that yesterday you saw a rose in your garden and stopped to inhale its fragrance. This event was processed by specific parts of your cortex at the brain's back and sides that are responsible for vision and smell. Today, if you recall the experience, those same regions will be reactivated. This idea, sometimes known as reinstatement, has been around for a while, but was only confirmed in the past decade or so, thanks to the development of brain scanning techniques. The same areas of the cortex light up in scanners both when someone first sees a picture of something and then is later asked to remember it.

A short-term memory of sniffing the rose wouldn't involve the hippocampi, as Molaison showed. But if, for some reason, you created a memory that lasted more than half a minute, then connections between the relevant areas of your cortex and your hippocampi would become strengthened. The hippocampi are wired up to many different parts of the cortex and help to glue together the different aspects of a single memory, says Spiers.

In fact, their role was beautifully illuminated this year. Researchers scanned people's brains as they tried to learn groups of unrelated concepts – such as Barack Obama with a wallet in a kitchen. They found that recall was best for those groups of concepts that had generated the most activity in their hippocampi during the learning phase. "The hippocampus allows you to retrieve all the elements together," says psychologist Aidan Horner at University College London, who did the study.

This ability helps explain one of memory's hallmarks – that recalling one aspect of an experience can bring its other features to mind unbidden. Hearing a song on the radio can remind us of the moment we first heard it, for example, or a long-forgotten taste of madeleine cakes can remind you of childhood. "It's almost as if we re-experience it," says Horner.

Intricate webs

I'm starting to get a picture of a memory as a discrete physical entity, a spider's web of silvery neurons firing together because of their strengthened connections, with strands reaching across different parts of the cortex and deep down to the hippocampi, guardians of our memory bank.

Yet something is still puzzling about the hippocampi. Research in rats and mice has shown they are crucial for navigation, with the structures sometimes even called the brain's satnav. By placing electrodes in the animals' hippocampi to see the activity of individual neurons, researchers discovered cells that fire only when an animal is in a certain location. These neurons are called place cells. Which combinations of these cells are firing can tell you where the rodent is to within 5 cm^2. "When the rat runs through a maze, you can see the cells fire in sequence," says Spiers. "Just through the rat's place cell activity, you can decode where it is – you're reading the rat's mind." He and others have found that the same place cells even fire when the rats are asleep, suggesting we are reading their dreams.

So how come long-term memory and navigation seem anchored in the same brain region? As Spiers sees it, navigation must have come first. "Every single moving animal that has to acquire food cares about the 'where' above all things," he says. Then, as mammals developed more complex intellectual lives, the hippocampi were co-opted into an all-purpose mechanism for anchoring any important event into our memories. "A grid system is a beautiful system for mapping lots of things on to," he says.

That's a fairly speculative idea, but it does have some support from work with people who have epileptic seizures originating in their hippocampi, as Molaison did. Nowadays only one hippocampus is ever removed. "And we always check the viability of the other hippocampus first," says neurosurgeon Itzhak Fried at the University of California, Los Angeles.

To pinpoint the problem area, patients often stay for a couple of weeks in his clinic with up to 100 electrodes in their ›

"THESE CHIPOLATAS SEEM AN UNLIKELY SEAT OF HUMAN LEARNING AND MENTAL TIME TRAVEL"

HOLD THAT THOUGHT

SHORT-TERM OR WORKING MEMORY involves retaining information for up to 30 seconds – long enough to dial a phone number, for instance – before it is forgotten. Short-term memory generally involves neuronal networks in the cortex, the outermost part of the brain.

LONG-TERM MEMORY involves holding information for longer than half a minute. It splits into *IMPLICIT* and *EXPLICIT* memories.

IMPLICIT (PROCEDURAL) MEMORIES are long term-memories involved in learning new physical skills, such as playing an instrument.

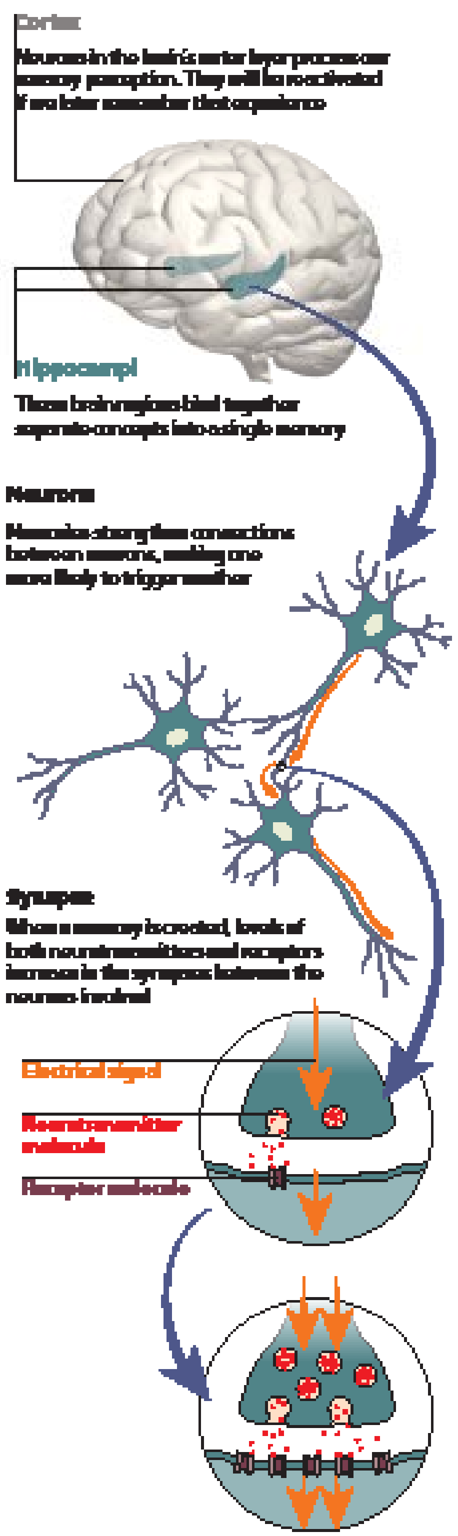
EXPLICIT (DECLARATIVE) MEMORIES are long-term memories we are aware of and can talk about. To create them, neurons in the cortex must activate others in the hippocampi, two structures deep in the brain.

Explicit memories take two forms: *AUTOBIOGRAPHICAL* and *SEMANTIC*

AUTOBIOGRAPHICAL (EPISODIC) MEMORIES are of specific events from our personal history, such as eating with a friend yesterday.

SEMANTIC MEMORIES relate to facts. They are thought to start out as autobiographical – we remember where and when we learned the fact. They then become semantic with repetition – we forget the personal context and just retain the fact.

You must remember this



hippocampi. Thanks to them we have discovered that, just as neurons in a rat's hippocampi fire only when the animal is in a specific place, so those in the human hippocampi fire only on recognising a certain thing. That could be a place but it could also be a person, an object or almost anything.

Fried's team popularised this idea in 2005 with the catchy notion of "Jennifer Aniston neurons", because one of their first patients happened to have an electrode placed next to a neuron that fired in response to pictures of the actor. But I thought that recognising people is the job of the visual cortex. So how does that tie into neurons in the hippocampi firing?

Jennifer Aniston

It all makes sense once I speak to Rodrigo Quian Quiroga at the University of Leicester, UK, who works with Fried. Different cells in the visual cortex are great at recognising the actor under different conditions – side on, with different hairstyles, under low lighting and so on. The hippocampi Aniston neurons, on the other hand, don't care about what she looks like; with them it's binary – she's either there or she isn't. They even fire when her name is spoken or written. "It's an abstract concept," says Quian Quiroga.

Here's how the two systems mesh: to form a lasting memory of seeing Jennifer Aniston on a particular occasion, the cortex neurons must fire up the hippocampi concept neurons. If you bumped into her while sightseeing at the Eiffel Tower, your hippocampi Aniston neurons would start firing at the same time as your hippocampi "Eiffel Tower neurons". That would strengthen the connections between them, helping to create a lasting association. At least, that's the theory, says Quian Quiroga. He and Fried have found some supporting evidence: when their patients with electrodes implanted in their brains were shown photoshopped pictures of Aniston in front of the Eiffel Tower, their Aniston neurons started to fire in response to pictures of the Eiffel Tower alone.

It's almost as if Quian Quiroga and his team are witnessing the birth of new memories in the brain. They may even be edging towards an answer to the question of how many neurons are involved. To do this they had to start with a couple of estimates: that there are about 1 billion cells in a human hippocampus and that we can recognise at least 10,000 different concepts, such as places, objects, friends or celebrities. When they showed a random selection of pictures representing such

SUZANNE CORKIN

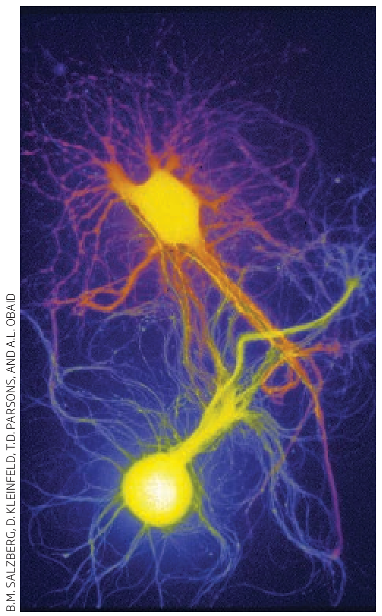
GROUNDHOG DAY EVERY DAY

What would it be like to have no long-term memory? The case of Henry Molaison, whose memory was damaged irreparably in 1953 after brain surgery for his epilepsy, gives us some clues.

Unlike the amnesiacs of movies, H.M. (as researchers called him) knew who he was, because he had retained most of his memories from before the operation. But he could hold no new information for more than half a minute. Researchers would have the jarring experience of him failing to recognise them after they had nipped out of the room for a moment.

If he saw his reflection, Molaison was often surprised by how old he looked. When his parents died, he forgot even that. Yet most of the time he seemed not frightened or confused but happy and good-natured. He often expressed a wish to further the cause of medical research and never tired of being tested. "He was always happy to help," says neuroscientist Suzanne Corkin at the Massachusetts Institute of Technology, who worked with him for nearly five decades.

As Corkin describes in her book, *Permanent Present Tense*, interactions with Molaison could verge on the surreal. On one car journey to the research centre, Molaison was sitting in the back seat when he noticed a McDonalds coffee cup on the dashboard. "Hey, I knew a fellow named John McDonald when I was a boy!" he said, and proceeded to tell a few stories about what they had done together. A few moments passed with Molaison looking out of the car window. Then he noticed the cup again. "Hey, I knew a fellow named John McDonald when I was a boy!" he said, and repeated the same tales, almost verbatim. Only minutes later, he did the same thing again. At that point, the researcher discreetly threw the cup under a seat.



B.M. SALZBERG, D. KLEINFELD, T.D. PARSONS, AND A.L. OBAID

A single concept may be represented by 1 million neurons in your hippocampus

concepts to their patients, they discovered that each neuron had about 0.1 per cent chance of firing in response to any given concept. This suggests that each concept is encoded by about 1 million hippocampi neurons.

In theory then, a memory of meeting Aniston at the top of the Eiffel Tower on my birthday should involve three different concepts and therefore some 3 million neurons in the hippocampi, according to Quian Quiroga. Wouldn't it also involve cells in the cortex – cells representing everything from my emotions and what I was wearing that day, to the sound of Aniston's voice? Perhaps, says Quian Quiroga, but not always. He points out that often our memories lack such details. "A skeleton of a memory is not as rich as we think," he says.

If he's correct, then my imagined silvery web of a memory with strands attached in the cortex and hippocampi changes with experience. As my memory of Aniston is adjusted, new links are made to the neurons in the hippocampi connected to Paris, and over time others are perhaps weakened.

I like this idea of memories as collections of concepts because it suggests they have a bigger role as the building blocks of thought. After all, how could I have thought about whether I wanted Spiers to make me a cup of tea when I was in his office unless I had the concept of tea, the memory of drinking it, and of liking it, stashed away somewhere? Talking about thoughts is too speculative for Spiers's liking, though. "They are a nebulous concept," he says.

But others are more willing to follow this line of thinking. They include Demis Hassabis, who leads Google's Deep Mind artificial intelligence venture and researches human memory in the hope it will inspire better artificial intelligence. He has found that people with damage to their hippocampi have as much difficulty imagining future events as recalling past ones, suggesting that memories play a significant part in the way we formulate thoughts. Breaking down the world into its underlying concepts may not just be the way that we think about the past, Hassabis says, but also the present and the future.

"MEMORIES ARE NOT JUST ABOUT THE PAST, BUT THE PRESENT AND FUTURE TOO"

It could even help us understand creativity. "If that's how memory works, then imagination must rely on the same processes," he says. "You're still pulling together components but in this case in a novel way." In that case, the way your memories tie together concepts and allow you to imagine things and plan your future defines you in an inescapable way. Without them, you couldn't desire a cup of tea, or dream up your perfect holiday.

So is it my memory that makes me me? I put the question to Hassabis. "Memories are core to ourselves and our personalities," he says. "It's a cliché that's also somewhat true – we are just the sum of our memories." ■

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