The physical trace of a single memory — also called an engram — has long evaded capture. US psychologist Karl Lashley was one of the first to pursue it and devoted much of his career to the quest. Beginning around 1916, he trained rats to run through a simple maze, and then destroyed a chunk of cortex, the brain's outer surface. Then he put them in the maze again. Often the damaged brain tissue made little difference. Year after year, the physical location of the rats' memories remained elusive. Summing up his ambitious mission in 1950, Lashley wrote[2]: "I sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning is just not possible."

Memory, it turns out, is a highly distributed process, not relegated to any one region of the brain. And different types of memory involve different sets of areas. Many structures that are important for memory encoding and retrieval, such as the hippocampus, lie outside the cortex — and Lashley largely missed them. Most neuroscientists now believe that a given experience causes a subset of cells across these regions to fire, change their gene expression, form new connections, and alter the strength of existing ones — changes that collectively store a memory. Recollection, according to current theories, occurs when these neurons fire again and replay the activity patterns associated with past experience.

Scientists have worked out some basic principles of this broad framework. But testing higher-level theories about how groups of neurons store and retrieve specific bits of information is still challenging. Only in the past decade have new techniques for labelling, activating and silencing specific neurons in animals allowed researchers to pinpoint which neurons make up a single memory (see 'Manipulating memory').

IN SEARCH OF THE ENGRAM

Josselyn helped lead this wave of research with some of the earliest studies to capture engram neurons in mice[3]. In 2009, she and her team boosted the level of a key memory protein called CREB in some cells in the amygdala (an area involved in processing fear), and showed that those neurons were especially likely to fire when mice learnt, and later recalled, a fearful association between an auditory tone and foot shocks. The researchers reasoned that if these CREB-boosted cells were an essential part of the fear engram, then eliminating them would erase the memory associated with the tone and remove the animals' fear of it. So the team used a toxin to kill the neurons with increased CREB levels, and the animals permanently forgot their fear.

A few months later, Alcino Silva's group at the University of California, Los Angeles, achieved similar results, suppressing fear memories in mice by biochemically inhibiting CREB-overproducing neurons[4]. In the process, they also discovered that at any given moment, cells with more CREB are more electrically excitable than their neighbours, which could explain their readiness to record incoming experiences. "In parallel, our labs discovered something completely new — that there are specific rules by which cells become part of the engram," says Silva.

But these types of memory-suppression study sketch out only half of the engram. To prove beyond a doubt that scientists were in fact looking at engrams, they had to produce memories on demand, too. In 2012, Susumu Tonegawa's group at the Massachusetts Institute of Technology in Cambridge reported creating a system that could do just that.

By genetically manipulating brain cells in mice, the researchers could tag firing neurons with a light-sensitive protein. They targeted neurons in the hippocampus, an essential region for memory processing. With the tagging system switched on, the scientists gave the animals a series of foot shocks. Neurons that responded to the shocks churned out the light-responsive protein, allowing researchers to single out cells that constitute the memory. They could then trigger these neurons to fire using laser light, reviving the unpleasant memory for the mice[5]. In a follow-up study, Tonegawa's team placed mice in a new cage and delivered foot shocks, while at the same time re-activating neurons that formed the engram of a 'safe' cage. When the mice were returned to the safe cage, they froze in fear, showing that the fearful memory was incorrectly associated with a safe place[6]. Work from other groups has shown that a similar technique can be used to tag and then block a given memory[7,8].

This collection of work from multiple groups has built a strong case that the physiological trace of a memory — or at least key components of this trace — can be pinned down to specific neurons, says Silva. Still, neurons in one part of the hippocampus or the amygdala are only a tiny part of a fearful foot-shock engram, which involves sights, smells, sounds and countless other sensations. "It's probably in 10–30 different brain regions — that's just a wild guess," says Silva.

A BROADER BRUSH

Advances in brain-imaging technology in humans are giving researchers the ability to zoom out and look at the brain-wide activity that makes up an engram. The most widely used technique, functional magnetic resonance imaging (fMRI), cannot resolve single neurons, but instead shows blobs of activity across different brain areas. Conventionally, fMRI has been used to pick out regions that respond most strongly to various tasks. But in recent years, powerful analyses have revealed the distinctive patterns, or signatures, of brain-wide activity that appear when people recall particular experiences. "It's one of the most important revolutions in cognitive neuroscience," says Michael Kahana, a neuroscientist at the University of Pennsylvania in Philadelphia.

"I CAN'T IMAGINE WANTING TO LOOK AT ANYTHING ELSE."

The development of a technique called multi-voxel pattern analysis (MVPA) has catalysed this revolution. Sometimes called brain decoding, the statistical method typically feeds fMRI data into a computer algorithm that automatically learns the neural patterns associated with specific thoughts or experiences. As a graduate student in 2005, Sean Polyn — now a neuroscientist at Vanderbilt University in Nashville, Tennessee — helped lead a seminal study applying MVPA to human memory for the first time[9]. In his experiment, volunteers studied pictures of famous people, locations and common objects. Using fMRI data collected during this period, the researchers trained a computer program to identify activity patterns associated with studying each of these categories.

Later, as subjects lay in the scanner and listed all the items that they could remember, the category-specific neural signatures re-appeared a few seconds before each response. Before naming a celebrity, for instance, the 'celebrity-like' activity pattern emerged, including activation of an area of the cortex that processes faces. It was some of the first direct evidence that when people retrieve a specific memory, their brain revisits the state it was in when it encoded that information. "It was a very important paper," says Chen. "I definitely consider my own work a direct descendant."

Chen and others have since refined their techniques to decode memories with increasing precision. In the case of Chen's *Sherlock* studies, her group found that patterns of brain activity across 50 scenes of the opening episode could be clearly distinguished from one another. These patterns were remarkably specific, at times telling apart scenes that did or didn't include Sherlock, and those that occurred indoors or outdoors.

Near the hippocampus and in several high-level processing centres such as the posterior medial cortex, the researchers saw the same scene-viewing patterns unfold as each person later recounted the episode — even if people described specific scenes differently[1]. They even observed similar brain activity in people who had never seen the show but had heard others' accounts of it[10].

"It was a surprise that we see that same fingerprint when different people are remembering the same scene, describing it in their own words, remembering it in whatever way they want to remember," says