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Dreamweavers

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The perfect memory is of everything and nothing

EVER since the unfortunate case of H.M., the subject of a lesion study second in fame only to that of Phineas Gage, neuroscientists have known that what the amygdala is to emotion, the hippocampus is to memory: if it is not the whole orchestra, then it is certainly the conductor.

H.M. lost the ability to form new memories when both of his hippocampuses were destroyed by radical surgery in the 1950s, and though he is now an old man, he still thinks of himself as the twenty-something who went into the operating theatre. He is palpably shocked whenever he sees himself in a mirror.

Memory is central to the question "who am I?" It is where the research is at its most nitty-gritty, with studies of the biochemistry of synapses and the action of individual genes, but also at its most esoteric, looking seriously at the function of dreams. It is, too, where cognitive neuroscience meets the videogames industry.

A few years ago Eleanor Maguire, of the Institute of Neurology in London, realised that her city has a resource available in no other large centre of population: taxi drivers who actually know where they are going. To become a London cabbie, you have to learn what is called the Knowledge: the location of every street within a 10km (six-mile) radius of the centre. This takes years of part-time study. If you fail the exam, you do not get a licence.

Dr Maguire and her colleagues used structural MRI (which predates fMRI, providing a static picture of anatomy) to study the hippocampuses of cabbies. They found that the shape of their subjects' hippocampuses varied with experience. As the Knowledge became consolidated, the back of the hippocampus seemed to grow while the front shrank.

With that result in their pocket, they have turned to videogames. One of the limitations of fMRI is that the scanners are heavy and unportable. But Dr Maguire wants to see what is going on in her taxi drivers' brains while they are using the Knowledge at work. So if the machine cannot travel around London, London has to travel round the machine. She makes this happen by employing a Sony videogame called "The Getaway" that can produce accurate representations of 110km (about 70 miles) of central London's roads. She uses it to project a lifelike image of driving round London onto a mirror visible from inside the machine. By this method, she is now studying how the hippocampus draws on other parts of the brain as her taxi drivers apply their Knowledge.

Knowledge or certainty?

Most researchers agree that long-term memory (as opposed to the short-term sort that can hold on to a telephone number long enough to dial it) comes in two varieties. One, known variously as explicit or declarative memory, records the salient details of an individual's life. For a taxi driver, the Knowledge is very salient. This form of memory involves the hippocampus. The other variety, implicit or procedural memory, involves the cerebellum and the basal ganglia. You may remember the anguish of individual violin lessons vividly via your hippocampus, but the finger movements required to play the instrument will be stored in your cerebellum. Even H.M. retains the ability to form new procedural memories, but his explicit memory has not grown since the time of his surgery.

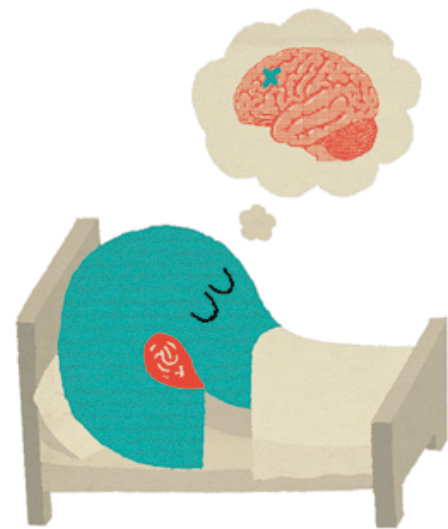
To complicate matters further, there are two types of explicit memory. One, known as autobiographical or episodic memory, records the experiences themselves. The other, known as semantic memory, tries to generalise from these experiences. And there is evidence, to which Dr Maguire is trying to add, that the former is stored in the hippocampus whereas the latter is consolidated in the cerebral cortex.

One of the researchers trying to tease out the distinction between the two is Matthew Wilson, of the Picower Institute for Learning and Memory in Cambridge, Massachusetts. The Picower is one of several foundation-funded brain-research institutes that have sprung up in America over the past few years. (Jeffrey Picower is a financier of biotechnology firms.)

Memory, as Dr Wilson observes, is like everything else in biology. It has evolved to serve a purpose and is honed for that purpose, which in this case is to react appropriately to the stimuli an animal meets in the environment by drawing on the experience of previous encounters. That is emphatically not the same as having a perfect memory for each of those encounters. Instead, memory should generalise from similar experiences and disregard the individual details. In other words, as time passes it should become more semantic and less autobiographical.

And indeed that is most people's everyday experience. The elderly are notorious for remembering every detail of their childhood but being unable to recall what they did last week. Such inability to remember details is often regarded as a failing, whereas so-called eidetic memory (or photographic memory, its more common name) is often admired by outsiders.

In Dr Wilson's view this perception is probably wrong. Indeed, an ideal memory would react like a behaviourist's black box. It would have generalised from experience to such an extent that individual events no longer need to be remembered at all; merely the appropriate response to the situation. So the fact that the elderly, who already have vast experience to draw on, do not waste precious storage capacity on adding things that will not aid their survival could well be the result of evolutionary adaptation rather than an indication of waning powers.



Dr Wilson studies memory formation by looking at rats. More specifically, he looks at rats dreaming—and day-dreaming—about what they have been up to. A connection between sleep, dreaming and the establishment of long-term memories has been known about for a while. Several years ago, he began recording the pattern of electrical activity in an animal's hippocampus as it learnt something about the environment, such as how to run round a particular maze, and showed that these patterns are recapitulated during what is known as rapid-eye-movement sleep, which in humans is the time for dreaming. This recapitulation seems to be crucial to memory formation.

He is now extending this work. He has shown that rats replay their experiences in their hippocampuses even when they are just resting, although, intriguingly, the pattern of electrical signals runs backwards at this time.

Learn in your sleep

Even more significantly, if electrodes are attached to neurons in the cortex that are connected to the hippocampus, part of the same pattern is seen there as well. However, there are differences between what is going on in the two places. When a rat is running a particular maze, the electrical pattern produced in the hippocampus is specific to that maze. Such patterns, though, share general features (similar corners in different mazes, for example, yield similar signals), and it is these general features that show up in the cortex. Dr Wilson interprets this as evidence of generalisation into semantic memory.

The recapitulation of experience in the form of neuronal firing patterns appears to be responsible for changing the pattern of synapses between nerve cells in ways that engrain particular memories by changing the way that information flows through the neuronal network. Dr Wilson's work does not explain exactly how those synaptic changes happen. But Elly Nedivi, one of his colleagues at the Picower, is one of those looking into the matter.

That long-term memory is encoded, at least in part, by changes in the strength of the synapses between nerve cells has been known since the pioneering work done by Eric Kandel of Columbia University in the

1960s and 1970s. Admittedly, Dr Kandel worked on a species of sea slug (an animal he chose because its neurons are easy to see and map), and at the time many of his contemporaries wondered whether the findings would hold true for more complex animals. But they did, and Dr Kandel's discovery of permanent changes in the strength and number of connections between neurons has become a cornerstone of the theory of memory.

Now, with the catalogues of genes provided by the Human Genome Project and its animal equivalents, it is possible to work out which genes are involved in these changes, and try to find out what they do. So far Dr Nedivi and her team have identified more than 360 genes that are unusually active in nerve cells during memory formation. They do this by looking for messenger molecules copied from genes in the nucleus and sent out to the protein-making apparatus in the cell body to tell it what to make. (It is these proteins that do the actual work in cells.) If particular messengers accumulate at synapses involved in memory, or seem to be associated with the growth of new axons and dendrites, that is a good indication that the proteins encoded by those messengers—and thus by the genes that generated them—have some role in the process.

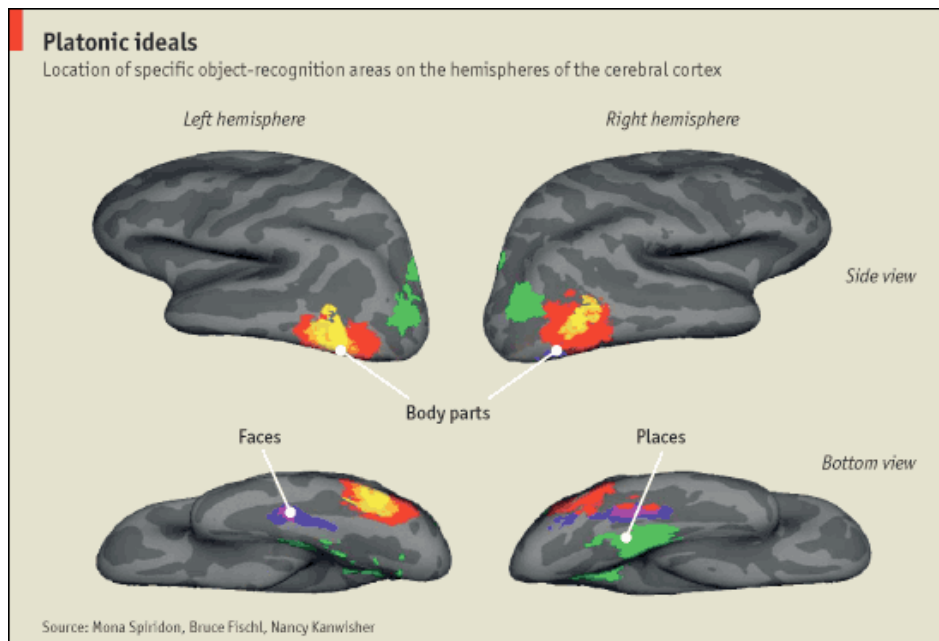
The next stage is to find out what that role is. Using a fancy piece of genetic technology that can slice any given gene out of the nucleus and eliminate it, Dr Nedivi is doing what are, in effect, nano-lesion studies, starting with a gene that seems to be involved in making dendrites grow (dendrite growth failure is a cause of several forms of mental retardation). Her hope is that each gene's precise role can be worked out by seeing what happens in its absence.

Plato's cave

Working at the other end of the neurological scale—and across a large atrium from the Picower Institute—is Nancy Kanwisher of the McGovern Institute for Brain Research. Like the Picower, the McGovern is a privately supported autonomous satrapy of the Massachusetts Institute of Technology (Pat and Lore McGovern are entrepreneurs who made their money, respectively, in publishing and in computing). Here, Dr Kanwisher uses fMRI to look at where, exactly, in the brain various things are recognised.

Dr Kanwisher's discoveries go some way towards addressing the question of Platonic ideals—in other words, what is the essential property that makes an object, say, a table rather than a pile of firewood. What she has found is that certain pieces of cortex are able to extract these essential properties and thus react very strongly to particular sorts of objects. There is, for instance, the fusiform face area, which responds strongly (and only) to faces. The extrastriate body area responds similarly to images of human bodies or body parts. And the parahippocampal place area responds to images of places.

This specialisation makes sense. Faces, body parts and places are all important categories of natural object. Dr Kanwisher's latest discovery, though, is particularly intriguing. It is that there is also at least one area that handles a specific category of artificial object: written words. It, too, is always in the same place (a part of the cortex called the left fusiform gyrus). Somehow, all healthy developing brains not only work out that written words are a category to which it is worth allocating its own piece of neural anatomy, but find it easiest to accommodate that category in the same piece of wetware.



That could not have evolved specifically. Writing is probably too recent for natural selection to have done its work, and mass literacy certainly too recent. Understanding how such circuitry forms would yield an important insight into the logic of the mind. It might also indicate that the other specialised areas found by Dr Kanwisher are the result of developmental processes rather than evolutionary hard-wiring.

At the moment, it is hard to understand how the different circuits of neurons in the brain relate to one another. But Susumu Tonegawa, the head of the Picower, thinks he may be able to get closer to the answer by using gene elimination of the sort employed by Dr Nedivi to manipulate the circuitry of the whole brain. The tool that will allow him to do this is a project called the Allen brain map. It is named after Paul Allen, Bill Gates's partner in the founding of Microsoft. Mr Allen is even richer than Mr Picower and Mr and Mrs McGovern, and he, too, has paid for his own institute, which is based in Seattle.

Initially, the Allen Institute for Brain Science had but a single mission, which it completed in September. This was to create and publish a map of where in the brain particular genes are active, so that other researchers could use it in the knowledge that it was complete. Admittedly the brain in question is a mouse brain. But the genes of mice and men correspond closely, as does much of their neuro-anatomy, and Dr Tonegawa is not proposing to carry out his experiments on people. He does, however, plan to put the map to use in a rather clever way.

Many genes are actually switches that control the activity of other genes. By identifying particular switches that are active in only one part of the brain, he can co-opt those switches into activating his gene eliminator. Thus particular genes can be eliminated from one place without affecting others. That means he can shut down individual nervous pathways in the brain without affecting the others.

This technique, which he has only just begun to use, will take the lesion method to a new level of refinement. Although anatomists can trace connections between various parts of the brain by following the axons, finding out what the connections are actually for is much harder. If Dr Tonegawa's technique works, such discoveries will be easier to make. The workings of the whole of the brain, not just the parts concerned with memory, will be laid bare.

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